persistent loss of vibration sense as prominent features of the condition may be of value in clinical usage. To call all these conditions "beriberi" only leads to pathological and therapeutic confusion. Arguments for and against the existence of thiamin deficiency in peripheral nerves (145) have accepted the premise that nearly all forms of peripheral neuritis are the same. The production of burning in the feet on the 5th day and cramps in the calves on the 7th day of experimental thiamin deficiency in human volunteers by Jollife and his associates (114) scarcely merits the term "polyneuritis" some have applied to the condition. Its significance remains to be explained, but it is extremely doubtful if it has any relation to true beriberi. Lastly, the assumption by some (180) (145) that pain after walking any distance in beriberi can be likened to intermittent claudication, and therefore indicates vascular change, is unwarranted in a condition where even slight contacts also cause pain.

2. Pellagra

Whereas the nervous symptoms under discussion bear doubtful, rare, and distant relationship to beriberi it is found that many of them have long had recognition in the symptom-complex of pellagra. Vertigo has been a classical feature of this condition since the earliest accounts. Pains in the hands and feet are common complaints. Billod described paraplegic disorders in 1865 (24). Taylor and Wood (236) state that a staggering gait is an early complaint which frequently persists through the whole course of the disease and is the last remnant in the recovering case. Besides the tremors and spasms which are so prominent in advanced states, increased tendon jerks, spastic rigidity in the lower extremities with ataxic gait and positive Romberg's sign are commonly described (24) (240) (19) (131) (100) (236) (23). In the "typhoid pellagra" of Belmondo (19) spastic changes with dysarthria and tremors characterize the final delirium. But it has also long been recognized that spastic or ataxic disorders of the lower limbs, and affections of the optic and auditory nerves, may in some patients occur early in the course of the disease. The plantar reflex is occasionally extensor, often on one side only. Roberts (187) found ataxia in 12 of 60 cases, vertigo in 20, slurred speech in 14. Deafness was present in 8 and vision impaired in 3. Tinnitus frequently accompanied the onset of deafness. Ellinger *et al* (71) found clinical evidence of spinal cord lesions in 10 of 39 pellagrins from Upper Egypt, and only in 4 per cent of patients from the Nile Delta. Lombroso (131) mentioned optic atrophy in 3 of 36 cases examined by Manfredi. Bietti (22) in 1901 found pallor of the optic disc in some cases but could not find any histological changes in the optic nerve in 2 cases followed to autopsy. He was inclined to believe that retinal degeneration accounted for amblyopia. Whaley (256) found optic atrophy in 3, and optic neuritis in 3, of 35 pellagrins. Bouchard (28) first described pigmentary changes in nerve cells and degeneration of the dorsal and lateral columns of the spinal cord in pellagra in 1864. Tonnini (240) found spasticity and exaggeration of reflexes common in the third stage of pellagra and described degeneration of the lateral columns of the cord in addition to the well known pigmentary degeneration of the anterior

horn and cortical cells. Langworthy (128) described diffuse degeneration of the lateral columns, with severe cell changes, in an acute case. Tuczek (242) saw combined, often vacuolated, degeneration of both lateral and dorsal columns of the spinal cord in 6 of 8 cases examined, the dorsal columns alone in 2. Belmondo (19) and Gaucher and Sergent (81) found degeneration in the dorsal columns, heavier in the cervical region. Sandwith (189) described diffuse degeneration of the posterior columns in 2 of 3 Egyptian cases. Lukás and Fabinyi (133), Marinesco (141), Anderson and Spiller (7), Box and Mott (30), Wilson (261), Singer and Pollock (210), McCowan (137), Greenfield and Holmes (93), and Pauly and Deprecq (176) all found diffuse degeneration in the lateral and posterior columns. Pentshew (178) found hyaline changes in the capillaries and considered that this and the patchy nature of degeneration indicated primary vascular factors. Winkleman (263) deals chiefly with the cell changes. Guillain and his colleagues (95) describe an example of severe combined degeneration of dorsal and lateral columns where spastic paraplegia long preceded cutaneous changes and stomatitis. Wood (275) pictures a severe vacuolated degeneration of the anterolateral and dorsal columns closely resembling subacute combined system disease. There is no mention of anemia, and the patient was aged 17 years. Wilson (261) found that some cases closely resembled combined system disease. Other accounts of the spinal degeneration in pellagra indicate a diffuse degenerative process unlike that accompanying pernicious anemia, and Anderson and Spiller (7) are particularly emphatic concerning this difference. Loss of vibration sense, which is a prominent feature of subacute combined system disease, is held to be prominent in pellagra by Taylor and Wood (236), but is not mentioned by others.

States of spastic weakness of the lower limbs with fascicular twitchings in the upper limbs are commonly described in terminal stages of classical pellagra. They appear to be due to the widespread scattered pigmentary degeneration of nerve cells. The more chronic spastic changes in the limbs do not resemble amyotrophic lateral sclerosis, for the dorsal columns are nearly always involved. The cell changes in the cerebral cortex in pellagra are more generalized and show ballooning of cells, and ill defined pigmentary changes, whereas those of amyotrophic lateral sclerosis are localized to the motor region and seldom show intermediate changes. Though muscular atrophy, fasciculation and twitchings are commonly present in late stages of pellagra, these are more diffuse and do not exhibit the slow spread of amyotrophic lateral sclerosis. Cases of pellagra with close clinical resemblance to amyotrophic lateral sclerosis (167), (23) are excessively rare and probably coincidence. Such changes in the peripheral nerves as have been described are limited to scattered loss of occasional fibers in anterior and posterior nerve roots (186) (121) associated with increase in π-granules (261) and irregular changes in the staining reaction of otherwise intact myelin by the Marchi method. No severe polyneuritis is commonly associated with classical pellagra, but the scattered degeneration of isolated peripheral nerve fibers corresponds with the scattered degeneration of isolated ventral horn and dorsal root ganglion cells (128). On the other hand cases of pellagra

seen in mental hospitals not infrequently show a combination of pellagra and true beriberi polyneuritis. The neuritis under these circumstances reacts to thiamine but not to nicotinic acid (212) (213) (144).

In many patients with signs of involvement of the nervous system clinical phenomena resembling combined system disease are intermingled with those recalling amyotrophic lateral sclerosis, and the pathology usually likewise presents both tract and cell changes. Examples of the more purely amyotrophic form are given by Tonnini (240), Langworthy (128) and perhaps the case of Greenfield and Holmes (93). The cases of Guillain (95) and Wood (275) and one of Tuczek's (242) cases represent the type most closely resembling combined system disease.

Of the various cutaneous manifestations of classical pellagra it may be noted that scaly dermatitis of the scrotum has often been described but used to be considered "atypical and infrequent" (275), although it appeared in 6 of the 11 original volunteers of Goldberger and Wheeler (88). Wood (275) mentioned that burning pains in the feet and hands were considered of bad prognostic significance. Burning of the feet was accepted as a symptom of pellagra by Stannus (220).

It has been recognized for a very long time that pellagra was a collection of syndromes rather than a disease (131) and that it could occur on diets lacking maize or corn. The recognition of the mucocutaneous changes of aribofla-vinosis and of niacin deficiency has left a variety of other dermatological, neurological and alimentary components of uncertain origin. Some neurological conditions associated with glossitis and stomatitis have been reported from various tropical countries. Despite the lack of the classical skin eruption Stannus (220) maintains that these are also pellagra. Since these special conditions are particularly germane to the disorders found in ex-prisoners-of-war, they will be discussed separately.

3. *Conditions Related to Pellagra*

Spinal ataxia in association with amblyopia (central scotoma), deafness and dysarthria and stomatitis was described by Strachan in 1897 (226) in Jamaica as a type of "neuritis" occurring in the workers on sugar plantations. He had briefly described similar symptoms in 1888 (225) but then emphasized burning sensations in the feet and desquamation without ataxia, associated with recurrent malaria. In the second report, he also considered the condition to be a malarial neuritis and since he mentions claw-hand contractures it is possible that beriberi complicated some of his cases. Stannus (219) noted the varying aspects of pellagra in natives in central Africa in 1912, and drew attention to the independent occurrence not only of stomatitis but also of loss of vision, deafness and ataxia. Scott in 1918 (196) described an acute form of the disease in Jamaica workers who lived exclusively on sugar cane during the harvest, and in this description, and also in the examples of the chronic disease described by Scott the condition was clearly independent of beriberi. Obstinate constipation was followed by the development of soreness of the eyes and mouth, then an as-

cending subjective numbness of the limbs associated with ataxic gait. In 3 of 21 cases described the onset of numbness of the feet was preceded by a burning sensation. Tactile and pain sensation was impaired. Localized muscular weakness and wasting did not occur. In no case was control of sphincters lost. The subjective numbness spread up the leg to the thighs, then to the hands, sometimes to the tongue. The knee jerks lessened and disappeared as the disease progressed and an initial exaggeration was observed in one patient. No extensor plantar response was observed. Amblyopia appeared late in the course of the disease, in 4 of 21 cases analyzed in detail, and deafness without vertigo or nystagmus was found in 2 cases. There was no strabismus and speech was not affected in the acute disease. On account of the predominant affection of kinesthetic sensation, the lack of muscular weakness or atrophy and the absence of cardiac affection the condition was not considered to resemble beriberi, which did not occur in the locality. The absence of mental change or cutaneous eruption was felt to exclude classical pellagra. Careful blood examinations were made but only a mild hypochromic anemia, unrelated to the severity of other symptoms, was found. Fatal cases succumbed to collapse after an acute diarrhoea of sudden onset, and 2 to 3 days in duration, late in the illness. In chronic forms of the disease amblyopia and partial deafness almost constantly accompanied the ataxia, and "a kind of dysarthria" was not uncommon. Diffuse Marchi degeneration of the optic nerves and of dorsal columns of the spinal cord and to a slight degree of the lateral columns was found at autopsy. The medical authorities of the island attributed this condition to a deficiency of protein in the diet, but Scott concluded that some unknown intoxication was more likely. It is of special interest that patients with the same prodromal symptoms who had diarrhoea in addition failed to develop the neurological syndrome.

In 1935 Landor and Pallister (126) investigated a condition previously thought to be a local variant of tabes dorsalis in Malayan convicts in Singapore and Johore. After 6 months of prison diet (parboiled rice with a moderate subsidiary diet containing a sufficiency of vitamin A and thiamin) pains and numbness in the legs developed with failing vision, and in some, photophobia. They give a detailed description of a sensory ataxia with impairment of sensation, with exaggerated tendon jerks until a late stage, and with amblyopia. Angular stomatitis and dermatitis of the scrotum were common. Residual central vision was as low as 6/60 with retention of pupillary reaction to light, and pallor of the temporal side of the optic discs was found in some. Blindness did not occur. Mental dullness was present in some but it was doubtful if it was more than could be accounted for by the physical incapacity. There was no sphincter disturbance. An impairment of general sensation was present in the lower limbs and could extend to the abdomen or even to the face. Romberg's sign was present in all 7 cases, but muscular wasting and foot-drop were absent. There was no cardiac disorder. Night blindness did not occur, there was no papular skin manifestation, no xerosis conjunctivae, and bowel disease was rare. No deafness or aphonia is mentioned. The spinal fluid was negative in 8 cases.

Gastric analysis showed achlorhydria in 4. A mild hypochromic anemia was common. There was no night blindness or phrynoderma. Yeast concentrates (Marmite) cleared the stomatitis and scrotal lesion but had a disappointing effect on the neurological condition. Liver and liver extract appeared to result in neurological improvement in early stages, and slight improvement was obtained with autoclaved yeast. In view of the absence of foot-drop, muscular wasting or tenderness in these cases, and the absence of beriberi for a long time in this region, the condition was held to be distinct from beriberi. The stomatitis and scrotal dermatitis led to its being called "avitaminosis B_2." In a later paper Pallister (173) described further cases in Chinese residents among the Malayan population. Stomatitis and scrotal eczema were followed by pains, numbness and weakness of the legs with dimness of vision, resembling the earlier series, except that the tendon jerks were later lost after an early brisk stage. The duration of the disorder was 2 months to $3\frac{1}{2}$ years in the 15 cases reported. Vibration sense was noted to be absent in 4 cases, touch sensation diminished over the lower limbs. One patient had a microcytic anemia, but few of the cases were anemic. Amblyopia was present in 5 of the 15, pallor of the disc in 2. There was no foot drop and no muscular tenderness. The diet consisted of polished rice, a very small amount of vegetables, fish, pork and sometimes beans. The small amount of animal protein is commented upon. The physical findings were as in the earlier series of cases. Treatment with yeast concentrates or fresh liver had little effect. It was now doubted if the condition had any relation to pellagra.

Meanwhile Fitzgerald Moore (157) described a condition of partial optic atrophy with sore tongue and scrotal dermatitis, associated with ataxia and mental disorder in native school children in Nigeria, fed on kassava, dried fish, oil and suet. Sore tongue and itching, scaling of the scrotum or vulva was followed later by dimness of vision with pallor of the temporal sides of the optic discs. In later papers (158, 159) cases in the general population were described. Retrobulbar neuritis was common and ataxia was an infrequent feature. Mistiness of vision was of sudden onset with photophobia. Total blindness did not occur. There was no xerophthalmia. The disease was considered curable in the early stages with yeast or yeast concentrates. Cod liver oil or fruit juice had no effect. The absence of eggs in the diet and the rarity of meat were noted. Kassava was eaten, but much less than formerly. Protein was considered the "missing link."

In the years 1932–1936 a number of medical officers in the British Colonial Service reported in the records of British Guiana (Brown) Sierra Leone (Wright), Barbadoes (St. John), Ceylon (Nicholls) similar syndromes of retrobulbar neuritis, ataxia and deafness and these are summarised by Stannus (220, 221) and Metivier (150). These reports all indicated that the conditions of retrobulbar neuritis, ataxia and deafness are independent of each other and of stomatitis, though all three occurred together in some degree. Photophobia was an inconstant feature, probably reflecting only the degree of ariboflavinosis present. Wright (276, 277) at first considered these conditions to be the result of vitamin

A deficiency, but the results claimed for yeast by Moore (159, 160, 161) led the conditions to be considered a type of ariboflavinosis (221).

Grande and Jiménez (89) and Peraita (quoted by Spillane (216)) are reported to have found conditions of paresthesias of the lower limbs, retrobulbar neuritis, ataxic paraplegia and "cochlear neuritis" among the inhabitants of Madrid during the siege of that city in the Spanish Civil War. The diet consisted mainly of bread, lentils, a little rice and garlic soup and was not especially low in thiamin content. Pellagra was extremely common though beriberi was stated to be rare. Yeast was reported to have a favourable effect on all these neuropathies, but vitamin A, thiamin, nicotinic acid and riboflavin were without effect.

Wilkinson and King (259) and Wilkinson (258) described stomatitis, glossitis, scrotal eczema, giddiness and weakness of the legs in Chinese refugees in Hong-Kong. The tendon jerks were usually exaggerated and associated with some degree of spasticity *with* extensor plantar responses. Some of these patients had dimness of vision, but this was rare. The condition was stated to be improved by yeast concentrates. Here the condition approximated closely to classical pellagra and the cord symptoms were spastic in type. There is no mention of sensory changes. An amblyopia of rapid onset without pain or mucocutaneous lesions also occurred at that time in Hong-Kong and was described separately (258). Response to nicotinic acid or riboflavin was said to be "spectacular" in bringing about a rapid expansion of the "concentric constriction of the fields of vision." It is stated that central scotoma could not be found but no other cause of the great loss of central vision was demonstrated.

Whitacre (257) mentions that American civilians in a Japanese internment camp had had paresthesias and "difficulty in focussing the eyes," and Adolph *et al* (4) found in another group of cases, besides pellagra and beriberi, a condition of chronic diarrhoea with failure of vision from central scotoma. Paresthesias and numbness of the lower limbs were frequent. Thiamin and nicotinic acid were not found to be effective in treatment but yeast brought about slow improvement in many, and in a brief trial riboflavin gave "promising" results.

Spillane and Scott (216) and Spillano (214) described a group of 112 cases of the same syndrome encountered in German prisoners-of-war in Allied hands in the Middle East in 1944. The condition appeared gradually and affected 61 cases with retrobulbar neuritis alone, 23 with ataxia in addition, 12 with deafness but no ataxia, and 9 with all three. Four cases had ataxia alone and 3 had retrobulbar neuritis, ataxia and laryngeal nerve palsy. The form of the retrobulbar neuritis and ataxia was identical with that in our cases, though no instance of extensor plantar response was encountered. The severe loss of vibration sense and general hypoesthesia of the lower limbs, at times up to the waist, is described. Few cases had mucocutaneous ariboflavinosis and there was no beriberi or scurvy at the time. The diet appeared to be fully adequate on paper but the cooking "far from ideal." Forty-nine cases of pellagra had occurred in the same camps in 1944. Yeast, yeast concentrate, riboflavin, nicotinic acid

and thiamin gave no benefit. Very slow improvement was noted when fresh liver and liver extract (both oral and intramuscular) were added.

Spillane (215) later examined some of the British cases from Burma and was convinced that the syndrome was identical with that found in the Middle East except that more of the patients had evidence of beriberi. Garland (80) also reported an impression of 10 cases in ex-prisoners-of-war from Burma, including some seen by us, and felt convinced that the condition was independent of beriberi and pellagra.

Butler and his associates (37) made a rapid nutritional survey of American civilian internees in Japanese camps on their return to an American port. The prevalence of edema without associated cardiac symptoms or signs is noted. Many had suffered from impairment of vision and a few still suffered from central scotoma. Loss of vibration sense was a frequent finding, attributed to "peripheral neuritis" in spite of the presence of the ankle and knee jerks in nearly all, and the presence of calf tenderness in few. It was concluded that "the most frequent residual of this deficiency state is peripheral neuritis. Many persons four months after an adequate diet still have evidence of such neuritis."

Clarke and Sneddon (52) report on 74 cases of neurological disability observed in 200 sick prisoners-of-war and internees repatriated from Hong-Kong. Of these 31 suffered from optic atrophy and ataxia, 21 from ataxia alone, 13 from optic atrophy alone, 6 from optic atrophy, nerve deafness and ataxia, and 3 from optic atrophy and nerve deafness. The conditions were evidently the same as observed by us, except that signs of macular degeneration in the fundi were observed. The macula appeared normal in my cases. Further in no case in their series did Clarke and Sneddon find extensor plantar responses. Many had in addition a manifest peripheral neuritis with foot-drop and muscular tenderness. One patient had aphonia, with facial weakness, wasting of interosseous muscles, "spastic scissor gait" with ankle clonus, but flexor plantar responses. No abnormalities of the blood or spinal fluid were found. There was lessened free acid on gastric analysis in some, hyperchorhydria in others. Some patients had developed fresh neurological symptoms (retrobulbar neuritis and ataxia) while under treatment with thiamin and nicotinic acid. It was concluded that some toxic agent or antivitamin factor was active. The tendency of symptoms to remain stationary after a certain maximum in spite of continuance of the same, or even worse, dietary conditions is commented upon. The average diets given in Hong-Kong camps are given. Compared with the data from Singapore these tables show less protein and carbohydrate, but rather more fat. These authors concluded that some unknown antivitamin in spoiled rice diet had probably interfered with carbohydrate metabolism.

Shapland (201) gives an ophthalmological report upon some of the cases of retrobulbar neuritis seen by us and some others. He illustrates the temporal pallor of the discs, but found no retinal changes. Vision had improved from 6/60 in both eyes to 6/36 R and 6/24 L following a prolonged course of multiple vitamin treatment in one case, from 6/60 to 6/18 in both eyes following treatment by marmite (yeast extract) in another. Shapland recommends Moore's treatment

of 1 drachm of marmite a day for 6 months (158). Shapland also noted that some patients had reported a worsening of visual acuity in the first weeks of liberation while on a full diet. This was not seen by us, though increase in edema on first return to a full diet was common.

It will be concluded therefore that the neurological conditions found by us certainly have had a widespread incidence in areas of marginal diets largely composed of cereals. The proportions of retrobulbar neuritis, ataxia and spastic symptoms have differed from one group to another. Our own group appears to have been the only one where definite extensor plantar responses in relation to a spastic element in the ataxia were observed, though spastic gait was clearly described in one of Wilkinson's (258) cases. The proportion of beriberi with foot-drop and muscular tenderness has also varied from group to group and was high in the cases of Clarke and Sneddon (52). The outbreaks reported by Scott, Landor and Pallister, and Pallister have presented the most purely ataxic syndromes, and only in Japan and Trinidad (Metivier) has retrobulbar neuritis occurred in relatively isolated form in large numbers. Deafness has appeared as an infrequent complication of the ataxic syndrome. The most varied views have been expressed as to causation of these disorders. Some hypothecate a toxic (196) or antivitamin (52) factor. Others (126, 221) ariboflavinosis, some are non-commital (216) though an origin in nutritional defect is generally agreed. Accumulated evidence from many countries substantiates the finding of Stannus (219) that these conditions are closely associated with parts of the syndrome of pellagra.

4. *Lathyrism*

The only purely spastic syndromes regularly ascribed to dietary fault are lathyrism and ergotism. The latter is distinguished by vascular cramps and gangrene, as early signs, of which a recent clinical description is given by Morgan (162). Paralysis resulting from the consumption of certain varieties of the lathyrus pea has been known since the time of Hippocrates (Book III) and was mentioned by the elder Pliny. The interesting reviews of Huber (103), Hamelin (98), Schuchardt (195), Stockman (222) cover its early history. It is stated (103) that the dukes of Wurtemberg decreed in the 17th century that no more than a third of pea flour should be used in making bread, a higher proportion being known to cause paraplegia.

In India lathyrism was described in a series of papers by Irving in 1859–1868 (107, 108, 109). The lathyrus pea (Khesari) is used more exclusively in famine years, though it is consumed in the form of reddish meals (Masur Dahl, or Harar Dahl) by many as part of the diet in normal times without effect. The disease is endemic in certain districts of northwest India and in Mysore in the south, but most of the sufferers date their affliction from famine years. Buchanan (34), Acton (2) and Young (285) give illustrations of the typical spastic paraplegia. McCarrison (134), Stott (224) and Shourie (207) describe other series of cases in India. An outbreak in France in 1829 caused by the consumption of bread containing over 50 per cent of pea flour was described by Despar-

and thiamin gave no benefit. Very slow improvement was noted when fresh liver and liver extract (both oral and intramuscular) were added.

Spillane (215) later examined some of the British cases from Burma and was convinced that the syndrome was identical with that found in the Middle East except that more of the patients had evidence of beriberi. Garland (80) also reported an impression of 10 cases in ex-prisoners-of-war from Burma, including some seen by us, and felt convinced that the condition was independent of beriberi and pellagra.

Butler and his associates (37) made a rapid nutritional survey of American civilian internees in Japanese camps on their return to an American port. The prevalence of edema without associated cardiac symptoms or signs is noted. Many had suffered from impairment of vision and a few still suffered from central scotoma. Loss of vibration sense was a frequent finding, attributed to "peripheral neuritis" in spite of the presence of the ankle and knee jerks in nearly all, and the presence of calf tenderness in few. It was concluded that "the most frequent residual of this deficiency state is peripheral neuritis. Many persons four months after an adequate diet still have evidence of such neuritis."

Clarke and Sneddon (52) report on 74 cases of neurological disability observed in 200 sick prisoners-of-war and internees repatriated from Hong-Kong. Of these 31 suffered from optic atrophy and ataxia, 21 from ataxia alone, 13 from optic atrophy alone, 6 from optic atrophy, nerve deafness and ataxia, and 3 from optic atrophy and nerve deafness. The conditions were evidently the same as observed by us, except that signs of macular degeneration in the fundi were observed. The macula appeared normal in my cases. Further in no case in their series did Clarke and Sneddon find extensor plantar responses. Many had in addition a manifest peripheral neuritis with foot-drop and muscular tenderness. One patient had aphonia, with facial weakness, wasting of interosseous muscles, "spastic scissor gait" with ankle clonus, but flexor plantar responses. No abnormalities of the blood or spinal fluid were found. There was lessened free acid on gastric analysis in some, hyperchorhydria in others. Some patients had developed fresh neurological symptoms (retrobulbar neuritis and ataxia) while under treatment with thiamin and nicotinic acid. It was concluded that some toxic agent or antivitamin factor was active. The tendency of symptoms to remain stationary after a certain maximum in spite of continuance of the same, or even worse, dietary conditions is commented upon. The average diets given in Hong-Kong camps are given. Compared with the data from Singapore these tables show less protein and carbohydrate, but rather more fat. These authors concluded that some unknown antivitamin in spoiled rice diet had probably interfered with carbohydrate metabolism.

Shapland (201) gives an ophthalmological report upon some of the cases of retrobulbar neuritis seen by us and some others. He illustrates the temporal pallor of the discs, but found no retinal changes. Vision had improved from 6/60 in both eyes to 6/36 R and 6/24 L following a prolonged course of multiple vitamin treatment in one case, from 6/60 to 6/18 in both eyes following treatment by marmite (yeast extract) in another. Shapland recommends Moore's treatment

of 1 drachm of marmite a day for 6 months (158). Shapland also noted that some patients had reported a worsening of visual acuity in the first weeks of liberation while on a full diet. This was not seen by us, though increase in edema on first return to a full diet was common.

It will be concluded therefore that the neurological conditions found by us certainly have had a widespread incidence in areas of marginal diets largely composed of cereals. The proportions of retrobulbar neuritis, ataxia and spastic symptoms have differed from one group to another. Our own group appears to have been the only one where definite extensor plantar responses in relation to a spastic element in the ataxia were observed, though spastic gait was clearly described in one of Wilkinson's (258) cases. The proportion of beriberi with foot-drop and muscular tenderness has also varied from group to group and was high in the cases of Clarke and Sneddon (52). The outbreaks reported by Scott, Landor and Pallister, and Pallister have presented the most purely ataxic syndromes, and only in Japan and Trinidad (Metivier) has retrobulbar neuritis occurred in relatively isolated form in large numbers. Deafness has appeared as an infrequent complication of the ataxic syndrome. The most varied views have been expressed as to causation of these disorders. Some hypothecate a toxic (196) or antivitamin (52) factor. Others (126, 221) ariboflavinosis, some are non-commital (216) though an origin in nutritional defect is generally agreed. Accumulated evidence from many countries substantiates the finding of Stannus (219) that these conditions are closely associated with parts of the syndrome of pellagra.

4. *Lathyrism*

The only purely spastic syndromes regularly ascribed to dietary fault are lathyrism and ergotism. The latter is distinguished by vascular cramps and gangrene, as early signs, of which a recent clinical description is given by Morgan (162). Paralysis resulting from the consumption of certain varieties of the lathyrus pea has been known since the time of Hippocrates (Book III) and was mentioned by the elder Pliny. The interesting reviews of Huber (103), Hamelin (98), Schuchardt (195), Stockman (222) cover its early history. It is stated (103) that the dukes of Wurtemberg decreed in the 17th century that no more than a third of pea flour should be used in making bread, a higher proportion being known to cause paraplegia.

In India lathyrism was described in a series of papers by Irving in 1859–1868 (107, 108, 109). The lathyrus pea (Khesari) is used more exclusively in famine years, though it is consumed in the form of reddish meals (Masur Dahl, or Harar Dahl) by many as part of the diet in normal times without effect. The disease is endemic in certain districts of northwest India and in Mysore in the south, but most of the sufferers date their affliction from famine years. Buchanan (34), Acton (2) and Young (285) give illustrations of the typical spastic paraplegia. McCarrison (134), Stott (224) and Shourie (207) describe other series of cases in India. An outbreak in France in 1829 caused by the consumption of bread containing over 50 per cent of pea flour was described by Despar-

anches (Hamelin (98)). Pierre Marie (140), Astier (12), Proust (182) and Grandjean (90) describe cases seen in Algeria in 1882 where a famine in the previous two years had led to greater consumption of lathyrus pea than usual. Cantani (41) described some Italian cases and first proposed the name lathyrism. Mingazzini and Buglioni (152) give an excellent description of further Italian cases with illustrations of the posture and gait. Trabaud (241) has described typical cases in Syria. Filiminoff (76) mentions a Russian outbreak. No reference to cases in Malaya, Batavia, the Philippines, China or Japan has been found.

The clinical condition is remarkably uniform in all these descriptions. The onset is most usually sudden, and the patient awakens one morning with pains in the lumbar region and finds the lower limbs weak and stiff. There may be slight fever. In the course of a few days there is further great reduction in motor power, and often paresthesias are felt in the lower limbs at this stage. In some cases the onset is more gradual, and tingling in the lower extremities may herald the onset. In a few days the legs are already spastic. Clonic tremors often accompany the spasticity and these are prominent in the upper limbs if the affection is severe. The pains and paresthesias disappear after the first week or two. There is usually no sensory loss, no clouding of consciousness or epilepsy (in early descriptions the spastic clonus was often described as epileptoid) and the control of sphincters is lost only when the condition was severe. Some degree of recovery of muscular power could occur after a single attack, but spastic extension of the limbs, with pes cavus and over-adduction left the spastic scissor-legged gait. Relapses occurred in some cases. Men are uniformly more susceptible than women.

Grandjean and Proust stated that sensation was lessened in some very severe cases. Cramps in the muscles were common. Peripheral gangrene resembling ergotism had been erroneously reported in early Algerian accounts but Proust, Astier, and Grandjean saw none in their patients. In one unsatisfactory autopsy on an Algerian case it was thought that softening of the lumbar spinal cord was seen (90). Filiminoff (76) cites an interesting case in a patient who acquired the disease in an outbreak during famine in Russia and survived 35 years. Burning of the feet was often prominent in the early stage. At autopsy an anterolateral sclerosis in the dorso-lumbar spinal cord was found. Buzzard and Greenfield (38) illustrate a similar anterolateral sclerosis with some degeneration of the column of Goll in the cervical region in addition. A vacuolated appearance of the degenerate areas gave some slight resemblance to the lesion of combined system disease.

Astier (12) states that his cases had consumed *L. cicera*, those of Grandjean *L. clymenium*, and noted that forms of cooking involving high temperature appeared to deprive the pea flour of its harmful effect. In some villages one person in every eight was affected. Of a group of persons on the same diet only a few were liable to develop symptoms. Astier believed that high humidity favored the poisonous effect. He described the characteristic gait, and stated that hyperesthesia and formication of the extremities were a constant feature

during the onset and in a few cases these sensations were replaced by anesthesia with loss of position sense and ataxia. The latter infrequent type of the disease resembled tabetic ataxia and the tendon jerks were then ultimately lost. Muscular atrophy was not observed but fibrillary tremors in the muscles were common. Speech, intelligence and vision were not affected. There were no skin rashes, and diarrhoea did not occur. Brunelli (33) called the condition "spastic tabes" but describes only the usual purely spastic paraplegia. The cases observed in Syria have been purely spastic and resulted from the consumption of *L. sativus* (241).

Simple spastic paraplegia without sensory loss has several possible causes, and only in its endemic form in relation to the consumption of lathyrus pea, and in the absence of evidence of syphilis (Erb's spastic paraplegia) of family history (familial spastic paraplegia), of association of the onset with acute exanthemata (post-vaccinal, post-measles, encephalomyelitis), and of history of the consumption of ergot is lathyrism reasonably certain. In an isolated case it is necessary to be sure that the paraplegia is not the first sign of focal disease of the spinal cord (multiple sclerosis, tumor). Minchin (151) however reports the common occurrence of spastic paraplegia in southern India in the region of Madras in Indian nationals on a diet very low in protein and vitamins, but not including lathyrus. There was no other clear evidence of deficiency. Twenty-one cases with spastic paraplegia are reported, with durations varying from 15 days to 3 years. The onset was sudden in 5, gradual in the others. Paresthesias accompanied the onset in 5, fever in 4. The spinal fluid and blood Wassermann reactions were positive in 1, negative in both in 16 others. A paretic type of gold curve was found in 5 (the gold sol tends to be unstable in India). The tendon reflexes were exaggerated with clonus and extensor plantar responses. The abdominal reflexes were present and equal in 12 of 21 and in 2 of these the upper limbs were also spastic. There was no affection of sensation and no abnormal vertebral calcification.

Shah (200) reported an outbreak of 64 cases of spastic paraplegia in a small Indian village in a part of India where the lathyrus pea was unknown. The onset was acute in 30, and preceded by nausea, vomiting or diarrhoea in 34. Paresthesias of the feet were common and some had analgesia or anesthesia of the feet. There was no glossitis or skin eruption, no affection of cranial nerves and no mental symptoms. The spasticity was accompanied by appropriate reflex changes but in late stages diminution of tendon jerks occurred, suggesting possible coincidence of a peripheral neuritis or dorsal column lesion. The patients maintained that wheat meal *chappatis* caused an increase in symptoms. Shah found the wheat of the preceding year contaminated with *Vicia sativa*, the vetch held to be responsible for lathyrism by Anderson *et al* (8). The description of this condition by Shah indicates more flexion of the knees than is usually seen but this was described also by Irving (107). We have observed old chronic cases in India with a spasticity of both flexors and extensors, resulting in slightly flexed posture of the knees, and consider this to be a matter of degree. Thus Shah appears to have established satisfactorily that spastic paraplegia

anches (Hamelin (98)). Pierre Marie (140), Astier (12), Proust (182) and Grandjean (90) describe cases seen in Algeria in 1882 where a famine in the previous two years had led to greater consumption of lathyrus pea than usual. Cantani (41) described some Italian cases and first proposed the name lathyrism. Mingazzini and Buglioni (152) give an excellent description of further Italian cases with illustrations of the posture and gait. Trabaud (241) has described typical cases in Syria. Filiminoff (76) mentions a Russian outbreak. No reference to cases in Malaya, Batavia, the Philippines, China or Japan has been found.

The clinical condition is remarkably uniform in all these descriptions. The onset is most usually sudden, and the patient awakens one morning with pains in the lumbar region and finds the lower limbs weak and stiff. There may be slight fever. In the course of a few days there is further great reduction in motor power, and often paresthesias are felt in the lower limbs at this stage. In some cases the onset is more gradual, and tingling in the lower extremities may herald the onset. In a few days the legs are already spastic. Clonic tremors often accompany the spasticity and these are prominent in the upper limbs if the affection is severe. The pains and paresthesias disappear after the first week or two. There is usually no sensory loss, no clouding of consciousness or epilepsy (in early descriptions the spastic clonus was often described as epileptoid) and the control of sphincters is lost only when the condition was severe. Some degree of recovery of muscular power could occur after a single attack, but spastic extension of the limbs, with pes cavus and over-adduction left the spastic scissor-legged gait. Relapses occurred in some cases. Men are uniformly more susceptible than women.

Grandjean and Proust stated that sensation was lessened in some very severe cases. Cramps in the muscles were common. Peripheral gangrene resembling ergotism had been erroneously reported in early Algerian accounts but Proust, Astier, and Grandjean saw none in their patients. In one unsatisfactory autopsy on an Algerian case it was thought that softening of the lumbar spinal cord was seen (90). Filiminoff (76) cites an interesting case in a patient who acquired the disease in an outbreak during famine in Russia and survived 35 years. Burning of the feet was often prominent in the early stage. At autopsy an anterolateral sclerosis in the dorso-lumbar spinal cord was found. Buzzard and Greenfield (38) illustrate a similar anterolateral sclerosis with some degeneration of the column of Goll in the cervical region in addition. A vacuolated appearance of the degenerate areas gave some slight resemblance to the lesion of combined system disease.

Astier (12) states that his cases had consumed *L. cicera*, those of Grandjean *L. clymenium*, and noted that forms of cooking involving high temperature appeared to deprive the pea flour of its harmful effect. In some villages one person in every eight was affected. Of a group of persons on the same diet only a few were liable to develop symptoms. Astier believed that high humidity favored the poisonous effect. He described the characteristic gait, and stated that hyperesthesia and formication of the extremities were a constant feature

during the onset and in a few cases these sensations were replaced by anesthesia with loss of position sense and ataxia. The latter infrequent type of the disease resembled tabetic ataxia and the tendon jerks were then ultimately lost. Muscular atrophy was not observed but fibrillary tremors in the muscles were common. Speech, intelligence and vision were not affected. There were no skin rashes, and diarrhoea did not occur. Brunelli (33) called the condition "spastic tabes" but describes only the usual purely spastic paraplegia. The cases observed in Syria have been purely spastic and resulted from the consumption of *L. sativus* (241).

Simple spastic paraplegia without sensory loss has several possible causes, and only in its endemic form in relation to the consumption of lathyrus pea, and in the absence of evidence of syphilis (Erb's spastic paraplegia) of family history (familial spastic paraplegia), of association of the onset with acute exanthemata (post-vaccinal, post-measles, encephalomyelitis), and of history of the consumption of ergot is lathyrism reasonably certain. In an isolated case it is necessary to be sure that the paraplegia is not the first sign of focal disease of the spinal cord (multiple sclerosis, tumor). Minchin (151) however reports the common occurrence of spastic paraplegia in southern India in the region of Madras in Indian nationals on a diet very low in protein and vitamins, but not including lathyrus. There was no other clear evidence of deficiency. Twenty-one cases with spastic paraplegia are reported, with durations varying from 15 days to 3 years. The onset was sudden in 5, gradual in the others. Paresthesias accompanied the onset in 5, fever in 4. The spinal fluid and blood Wassermann reactions were positive in 1, negative in both in 16 others. A paretic type of gold curve was found in 5 (the gold sol tends to be unstable in India). The tendon reflexes were exaggerated with clonus and extensor plantar responses. The abdominal reflexes were present and equal in 12 of 21 and in 2 of these the upper limbs were also spastic. There was no affection of sensation and no abnormal vertebral calcification.

Shah (200) reported an outbreak of 64 cases of spastic paraplegia in a small Indian village in a part of India where the lathyrus pea was unknown. The onset was acute in 30, and preceded by nausea, vomiting or diarrhoea in 34. Paresthesias of the feet were common and some had analgesia or anesthesia of the feet. There was no glossitis or skin eruption, no affection of cranial nerves and no mental symptoms. The spasticity was accompanied by appropriate reflex changes but in late stages diminution of tendon jerks occurred, suggesting possible coincidence of a peripheral neuritis or dorsal column lesion. The patients maintained that wheat meal *chappatis* caused an increase in symptoms. Shah found the wheat of the preceding year contaminated with *Vicia sativa*, the vetch held to be responsible for lathyrism by Anderson *et al* (8). The description of this condition by Shah indicates more flexion of the knees than is usually seen but this was described also by Irving (107). We have observed old chronic cases in India with a spasticity of both flexors and extensors, resulting in slightly flexed posture of the knees, and consider this to be a matter of degree. Thus Shah appears to have established satisfactorily that

blindness, stomatitis or other evidence of deficiency than in areas where lathyrism did not occur.

Though the rapidity of action of lathyrus pea, the limitation of the syndrome to this particular diet and its common occurrence in herbivorous animals tend to indicate a directly toxic effect rather than a deficiency disease, the uncertainty of its occurrence appears to indicate some particular liability in the metabolism of the sufferer. Mellanby (146) has pointed to similar uncertainty in the experimental production of paralysis by ergot, which was much more directly effective if vitamin A deficiency was present, and suggested a similar mechanism for the production of lathyrism. *Lathyrus sativus* did not cause paralysis in rat experiments of McCarrison and Krishnan (135). In feeding experiments in rats Basu *et al* (17) found both the field pea and *L. sativus* lower in biological protein values than soya bean, and the proteins of lathyrus were much inferior to either of the others in growth promotion. Basu *et al* (18) found that the proteins of *L. sativus* are deficient in tryptophane. Deficiency in tryptophane in rats is reputed to cause loss of weight, nervous tremor, incoordination in movement, lumbar kyphosis and death in convulsions (1) but the subject requires reinvestigation in the light of more recent knowledge of the B complex. Geiger *et al* (82) found that rats fed on the ornamental sweet pea (*Lathyrus odoratus*) developed a similar kyphosis with deformity of the long bones and weakness in the limbs which was called "lathyrism" but which bears little resemblance to human lathyrism. The noxious principle was heat resistant and water soluble. The accompanying nervous disorder in the rat had nevertheless a striking resemblance to the condition originally described in egg white injury (25) but not now recognized as part of biotin deficiency, and there is likelihood of some common factor as yet not understood. It may be recalled that Sure (230) in 1921 found that the proteins of *Vicia sativa* were biologically of low value, but that some substance in zein corrected the fault. This author eliminated tryptophane, lysine, tyrosine, alanine and proline and concluded that it was some as yet undetermined substance.

It is therefore not by any means conclusive that lathyrism has ever been experimentally produced and studied, or that the disorder is produced by *lathyrus sativa per se*. It is certainly possible that lathyrus meal has the same relationship to the appearance of spastic paraplegia as corn grits have to the causation of "black tongue," namely a neutralisation of the action of a vitamin (niacin in the case of "black tongue") through the absence of tryptophane (99) (123) (124). If this is true the nature of the remainder of the diet is of first importance. If some toxic anti-vitamin substance is present as has been suggested by Jiménez Díaz and his colleagues (112) it is remarkably inconstant.

5. *"Burning feet" and Acrodynia*

"Burning of the feet" has been observed for many years in Bengal, Burma, Siam and Singapore (184). It has been regarded as the result of malaria by some, as a variety of beriberi by others. It occurred in 1826 in the first Burma war (94) (139) (254). Malcolmson (139) clearly distinguished the condition

from beriberi, and remarked on the accompanying sensation of numbness, and the usual absence of edema or other signs of vascular disorder. The skin was usually dry, and in a few cases a scaly rash with fever was mentioned. Previous diarrhoea was common. All observers agreed on the intensification of burning at night, and some remark on relief by cooling. Any covering on the feet was unbearable. The sensation may in severe cases spread to involve the hands, or over the whole body (139). "Burning of the feet" and beriberi seldom occurred together in the same patient. In uncomplicated beriberi pain may be in the nature of a gnawing ache or soreness, and extreme tenderness of the calves, sometimes of the instep, is characteristic. Burning sensation is sufficiently rare to be a coincident other condition. Chevers (45) remarks on sloughing of the cornea in some of his patients, which is of special interest in relation to the association of burning feet with the degeneration of the cornea reported in Changi Camp in Singapore in 1943 and the same association reported by Metivier (150). The diarrhoea is described as being chronic and both it and the sensation of burning were unduly persistent in the face of all manner of treatments. Malcolmson (139) remarked on the monotony of the fish and rice diet of soldiers developing the disorder and found transfer to a dry climate with full diet to result in slow recovery.

Burning sensations in the feet were the prominent feature of an epidemic outbreak in Paris in 1828 and 1829 for which Chardon (44) proposed the name "Acrodynia." Forty thousand persons are stated to have been affected at the height of this epidemic, of which the chief features were burning pain and numbness of the feet and hands, worse at night, vomiting or nausea at the onset, followed by persistent diarrhoea and an erythematous rash and occasionally a dark pigmentation of the skin. Desquamation was frequent. Conjunctivitis was common and superficial keratitis occurred in a few cases. There was no mental disorder. The condition, of which a number of contemporary descriptions were made, was reviewed by Vidal (250) in 1864, who mentions earlier epidemic outbreaks in Italy ("Pedionalgia") and later in Belgium. The diet was considered to be blameless, but it is clear that the possibility of intoxication related to ergot was the chief consideration excluded.

Only sporadic attention has been given to this subject in recent years. It is doubtful if the symmetrical burning sensation in the hands as generally termed "acroparesthesiae" has any relation to the earlier disorder. Instead, attention has been focussed on the affliction of infants called "pink disease" or "erythroedema" described first by Swift and by Wood (274) and called "acrodynia" by many. The rash, the photophobia, and an emphasis on affection of the hands are here more prominent than has been described in the burning of the feet of adults, and the pink cold extremities entirely different. No visual defect is described, but weakness of the limbs with scattered degeneration of nerves and axonal changes in anterior horn cells are established (175) (281) (118).

The adult condition of "burning feet" or "acrodynia" was however described by Sharples (202) in 1929 in laborers on sugar plantations in British Guiana. The patients were Hindu women between the ages of 17 and 40. The burning

began in the soles of the feet and when severe extended to the tips of the fingers. In very severe cases there was dimness of vision and loss of tendon jerks. In no cases did an extensor plantar response occur. There was no anemia. Here, then, the condition preceded and outnumbered the retrobulbar neuritis—ataxic syndrome.

Metivier (150) described in detail and illustrated a condition of "corneal epithelial dystrophy" associated with burning sensations in the feet in patients in Trinidad. The condition of retrobulbar neuritis with ataxia was also occurring in the same locality, but this and the corneal condition coincided in few patients. The diet was chiefly milled cereals and starchy foods but beriberi and pellagra were excessively rare. The corneal dystrophy responded rapidly to treatment by riboflavin and slowly to yeast concentrates. Pallister (173) also mentioned briefly a condition of burning feet seen in Indian labourers in Malaya often with brisk tendon reflexes, and some with ataxia, also described briefly by Dugdale (66). The condition was common in prison camps in Singapore and also Hong-Kong (52).

Dychitan (68) gave an account of the disorder called "Lapnus" (lit. peeling) which occurred in poverty-stricken natives on a rice diet on the Philippine island of Mindoro. It prevailed in the hot weather with a mortality of over 50 per cent. Stomatitis was common. Burning of the soles of the feet was followed by cyanotic discoloration and later peeling of the skin of the feet and hands. Weakness of the limbs with increased tendon jerks then preceded mental apathy and often there was opacity of the cornea. Deafness occurred in some cases. Katz (117) describes a similar condition in American prisoners in the Japanese camp at Cabanatuan in Luzon except that the condition is described as "tenderness" of the feet and hands with erythema, desquamation and impaired intellectual function, altered tendon reflexes, and retrobulbar neuritis. This variant of the syndrome more closely corresponds with "pink disease" in children and leads to suspicion that the Philippine disease is different from the others described.

There is good evidence therefore, that burning of the feet with or without corneal degeneration is a separate entity associated with an exclusively cereal diet. The corneal degeneration is probably closely related to Westhoff's disease ("tropical punctate keratitis") and similar outbreaks of corneal degeneration discussed by Elliot (72). Nocturnal burning of the feet is not uncommon in elderly people in temperate climates (the "causalgie nocturne spontanée des vieillards" of Tinel (239) and "pseudo-erythromalalgia" of Craig and Horton (58). This condition is discussed in relation to other minor paresthetic syndromes of the legs by Ekbom (70) in an interesting thesis on nocturnal restlessness of the lower limbs (anxietas tibiorum, asthenia crurum paresthetica). These syndromes are undoubtedly common and merit further attention.

6. *Myasthenic Bulbar Paralysis*

Musselman (164) reports an outbreak of "a symptom complex similar to myasthenia gravis" in late 1944 among American prisoners of war in Cabana-

tuan. Tiring of the eyes and blurring of vision at the end of the day preceded the onset of ptosis of the eyelids, diplopia and weakness of the muscles of the face and neck. Dysarthria and dysphagia then appeared. The arms and legs were affected in some cases. Some observers thought that a poison from dried fish was the cause, but some patients had not eaten fish. Improvement occurred with rest, a restriction of salt in the diet, and the administration of potassium chloride and thiamin. An outbreak of dengue had preceded the appearance of this syndrome, but no such disorder has been reported after dengue elsewhere. Katz (117) also describes this condition in the same group of patients in greater detail, and adds that it occurred 15–24 days after an epidemic of dengue, and affected only those who had had a mild attack of fever. In some the cell count in the spinal fluid was increased, not in others. Many were feverish. The tendon reflexes were diminished. Large amounts of Philippine cassava root and some poorly preserved salt fish had been consumed, and recovery was prompt after the daily protein was raised to 100 gm. He also describes the occurrence of sudden flaccid weakness of the arms and legs with diminished tendon reflexes without cranial nerve symptoms in another group of patients at an earlier date. This condition responded to prostigmine in 15 minutes, to potassium in 4 to 5 days. The only cases reported in Burmese, Malayan or Batavian camps were the 3 patients seen by Graves in Changi Camp, mentioned earlier. Here dengue was not a factor and salt fish not specifically mentioned, but tapioca in large quantities had unbalanced the diet in each case. The descriptions given by Musselman and Katz strongly suggest identity of the disorder with Gerlier's (83) "vertige paralysant" of which outbreaks occurred in Switzerland in 1886. There was no true vertigo in this affection and Gerlier's use of the word referred to the periodic sudden weakness of the extensors of the neck induced by fatigue (83) (60). All descriptions of the affection present the feature of paralysis after the use of muscles, strongly suggesting a myasthenic muscular bulbar paralysis rather than a central nervous disorder. We have found the same disorder described as endemic in the northeast island of Japan by Miura (154) in 1896. It was called "Kubisagari"* (lit. "one who hangs his head"), and the symptoms included dimness of vision (40 times in 63 cases) and hyperemia of the optic disc. Ptosis was present in 38 cases, paresis of cervical muscles in 34, diplopia in 29, paresis of the limbs in 26, of the tongue in 16. The acute attacks lasted from several minutes to several

* Through the courtesy of Capt. Daniel Sciarra, MC, U. S. Army, and Dr. Miura himself, it has been ascertained that cases of Kubisagari have not been observed, even in the prefecture of Gomori where it was formerly most common, since 1933. Older practitioners in the area still remember the disease, which retained the characteristics originally described by Miura. According to Dr. Miura, a further description of the disease was given by Saburo Inouye, *"On the Kubisagari-Disease," in Japanese, in Biorigaku-Kiyo (Review* of Pathology) Vol. 2, No. 1, January 1925. The spinal fluid was normal in cell and protein content but had a slightly raised pressure in eight of ten cases. The Wassermann reaction was negative in all. Blood, urine, and feces showed no abnormality. Dr. Miura and others now regard the disease as the result of an unknown dietary defect. Relief of symptoms was obtained by inclusion of eggs in the diet.

hours and were induced by exertion or by hunger. The tendon reflexes were increased. In no case was the disease fatal even after many years; an important difference from myasthenia gravis. No deafness is mentioned. It had been seen only in peasants living in close proximity to cattle and had been thought to have possible relationship to cattle plague. The circumstances of its appearance in prisoners-of-war, negative findings in blood and spinal fluid examination and the relationship to cassawa in one outbreak and tapioca in another all indicate that dietary defect should be considered.

One is reminded of a curious statement by Marshall (142) in one of the early descriptions of "beriberi" in Ceylon in which he comments that the muscles of the back of the neck are affected and eventually the powers of articulation are much impaired. The other elements of the description indicate classical beriberi, both cardiac and neuritic.

Several investigators have found that thiamin inhibits cholinesterase (11) but if deficiency in thiamin results in over-rapid destruction of acetylcholine a myasthenic syndrome would be commonplace. Some other factor is clearly necessary.

IV. LESIONS REPORTED IN EXPERIMENTAL ANIMAL DEFICIENCIES

Mellanby (146, 147) demonstrated that spastic ataxia and various cranial nerve lesions resulted from feeding diets basically of wheat germ, rye germ or white maize, and prevented by substances such as butter, mammalian liver, oil and egg yolk. He found that ergot intensified the degeneration, and that carotene prevented the effect of ergot. Since the earlier preventive substances were all rich in vitamin A the degenerative lesion in the cord on wheat germ and white maize diet was considered to result from vitamin A deficiency. Later it was shown that degenerative changes in the nerves and spinal cord of young growing animals resulted from the bony overgrowth and distortion associated with pure A deficiency (271) (148). In a review of the subject Wolbach and Bessey conclude that (272, page 237) "the nervous lesions of vitamin A deficiency thus are wholly mechanical in origin." Blindness and deafness may thus be accounted for by deformity of the bony foramina of the skull. In the neurological syndromes that occurred in prisoners-of-war no such bony changes were found, and xerophthalmia, the accepted index of vitamin A deficiency, was extremely rare at any time.

Whereas the classical experiments of Eijkman in 1896 demonstrated the production of polyneuritis in fowls by feeding on highly milled rice, and Fraser and Stanton (77, 78) and Vedder and Clarke (249) showed that rice polishings prevented its occurrence, some in recent years have doubted the part played by *thiamin* deficiency in production of the neuritis of beriberi. Neuritis is reported to have occurred in rats receiving thiamin in addition to an unbalanced diet (Vedder (246, 247, 248)). The rat, however, is particularly resistant to thiamin deficiency and the effects are central (48) so that the significance of such experiments is difficult to evaluate. Wintrobe *et al.* (270, 266) found it impossible to produce polyneuritis in swine by thiamin deficiency. Doubts have arisen

over the long delay or absence in recovery of polyneuritis in man in spite of thiamin treatment (145, 214, 266, 246). Vedder and Clarke (249) in their early experiments on polyneuritis gallinarum had shown that even with rice polishings (and therefore both known and unknown protective substances) the rate of recovery was directly proportional to the chronicity and severity of the original symptoms. The symptoms of acute thiamin deficiency are in contrast certainly reversible with great rapidity by thiamin, but such symptoms are in the nature of a disorder of the righting reflexes and other disorders of function associated with minimal lesions in the brain stem (232) (181). Swank (231) showed that only when the deprivation of thiamin is less complete does polyneuritis appear, but its appearance was then completely preventable by the administration of greater amounts of thiamin with the same diet in pigeons. The largest and longest nerve fibers in the peripheral nerves were found to degenerate first and in severe grades of disorder the degeneration extends proximally to involve nerve roots. Degeneration of the central prolongation of the sensory neurones of the dorsal root was followed into the dorsal columns of the spinal cord in severe states and some dorsal root ganglion cells were destroyed. Recovery is then limited by the destructive aspects of the lesion. In the pigeon some spino-cerebellar fibers also degenerated. All these changes have been found in severe human beriberi. Covell (56) found slight changes in the organ of Corti in thiamin deficient animals, but demyelination was "slight or negligible" compared with the much greater change induced by riboflavine deficiency. Reduction in vision is reported to be mentioned by Marchesini quoted by Spillane (214) but the evidence of Kagawa on human cases, mentioned in the previous section, leaves considerable doubt as to the relationship of visual loss to thiamin defect.

The occasional occurrence of "spasticity" in the polyneuritic fowl during treatment with whole rice was noted in 1911 by Chamberlain and his associates (42). No cord lesion was found. Similar clonic spasms and "spasticity" in the hind limbs of thiamin deficient dogs, associated with convulsions in some was described by Cowgill (57) and Street *et al.* (229). This condition cannot be accepted as a thiamin deficiency for it tended to become more manifest in a stage of partial recovery following intravenous administration of thiamin. No central nervous lesion was found except the dorsal column lesion accompanying neuritis. Occasionally the spastic phenomenon failed to appear, then being replaced by the classical flaccid polyneuritis (57). It savors strongly of defect in pyridoxine and pantothenic acid (see below), but further investigation is obviously needed.

Since some have questioned the relationship of the polyneuritis of beriberi to simple inanition it may be indicated that in their original studies Fraser and Stanton (78) showed that fowls subject to simple inanition generally survived longer than those fed on white rice and failed to develop neuritis. Others have since made similar and conflicting observations, obviously depending on the degree of inanition and of thiamin deficiency. Others report degeneration of nerves in simple starvation. In material examined by the Marchi method alone blackening of segments of myelin of undegenerated fibers is common after starva-

tion (231). This change is also well known in pellagra (the "Bandstreifen" of German authors) and cannot be accepted as equivalent to neuronal degeneration. Though thiamin deficiency is difficult to produce in the rat polyneuritis does then occur (62), being difficult to differentiate from starvation effects. Recently Shaw and Phillips (204) report some degenerative changes in nerves in simple inanition in chickens, with Marchi and Bodian stains, but nothing comparable to that of thiamin deficiency.

Deficiency in *riboflavin* also differs in its effects according to its degree. In its most acute form in the dog it is evidenced by sudden collapse and death in coma in 12 to 24 hours following the onset of symptoms (198) which may include bradycardia, weakness and ataxia with hyperactive reflexes and convulsions. The *rapid onset* of the nervous symptoms in a few hours is notable. Dermatitis of the scrotum was present and had developed gradually. There were extensive changes in nerve cells in the central nervous system, some diffuse myelin damage to the pyramidal tracts and fasciculus cuneatus in the spinal cord, and degeneration in the 9th and 10th cranial nerve roots. The heart muscle was normal. In more partial chronic deficiency Zimmerman *et al.* (288) (286) found the gradual development of an ataxia in dogs, without spasticity, which took some 500 days to develop. Degenerative changes were found in the peripheral nerves, the dorsal nerve roots, and the extension of them into the dorsal columns of the spinal cord. Phillips and Engel had found similar changes in chicks deficient in riboflavin, but in a later communication (179) it was concluded that the central nervous lesion was due to a related deficiency in pantothenic acid. Wolbach and Bessey (272) have reviewed this and subsequent work and doubt if the nervous lesions of such long latency were the direct consequences of riboflavin deficiency. Riboflavin however is essential to several enzyme systems (73) and it is possible that these may be independently disturbed.

Though inadequacy in *nicotinic acid* has been established as the chief dietary defect leading to the glossal lesions of pellagra it is highly doubtful if any degenerative lesion of the nervous system can be attributed directly to this deficiency. Very slight degenerative changes have been observed in the dorsal columns of the spinal cord (287) as very late and probably indirect manifestations without symptoms.

Deficiency in *pyridoxine* besides producing the distinctive dermatitis of the paws, snout and ears of the rat, preceded by erythema and edema described by György as "rat acrodynia" (96), is associated with convulsions, (47). In the pig Wintrobe *et al.* (264) found a severe microcytic anemia and both major and minor seizures, with fatty infiltration of the liver. Cardiac embarrassment and degenerative changes in the peripheral nerves and spinal cord were reported in dogs (228) after nearly a year of diet free of pyridoxine and without skin changes. Others (10) (272) have found no lesions in the nervous system in severe deficiencies. Antopol and Tarlov (9) described degeneration of the dorsal roots in rats and dogs receiving massive doses of pyridoxine. This finding suggests the necessity for some balance between pyridoxine and pantothenic acid and possibly thiamin but the mechanism requires further investigation.

Pantothenic acid is a filtrate factor in yeast and liver and is essential for growth

and well-being in many species. Deficiency in the rat leads to hemorrhagic cortical adrenal necrosis, and in chicks a dermatitis. Paralysis, with degenerative changes in the sciatic nerves and spinal cord of the mouse was reported by Lippincott and Morris (129) and in the spinal cord of the chick by Phillips and Engel (179). Shaw and Phillips (203) confirm the degeneration in all columns of the cord in chicks, especially the lateral and anterior tracts from the cervical to the lumbar region, without peripheral nerve lesions. Wintrobe and his associates, in a long series of researches on the remarkable ataxia of swine (268, 265, 269, 267) found a degeneration of the dorsal root ganglion cells with both the peripheral and central processes of the sensory neurones, to be due to deficiency in pantothenic acid and preventable by this factor and to a greater extent by raw liver, which contained pyridoxine as well. These authors also found similar ataxia to result from pyridoxine deficiency in swine.

Biotin deficiency, at one time thought to be related to the onset of spastic paralysis in animals suffering from "egg white injury" (25) seems now to be held responsible for only a scaly dermatitis of the whole body, especially the face, arms and legs (252) (203). No lesions in the cord or nerves have been found in folic acid deficiency (203). The central nervous degeneration originally reported in states of deficiency of *vitamin E* (wheat germ oil) are suspected of being related to some contaminating deficiency (174) (272).

Although the variation in daily requirement of thiamin according to the amount of carbohydrate metabolism is well understood (31) (57), the influence f other factors in metabolism on the availability of vitamins has recently asumed some importance. The influence of deficiency in tryptophane in preenting the effect of available niacin (99) (123) (124) has been mentioned earlier. ecent proofs of *anti-vitamins* are also notable. Chastek paralysis, an acute ietary disease in foxes fed on raw fish has been shown to be due to the presence, f an antithiamin enzyme (91). This enzyme is present in fresh water fish, ut also some salt water fish such as the Pacific mackerel and Atlantic clam 149). It is destroyed by heat (217) (149) and therefore by cooking. Though sh was commonly consumed in prisoners-of-war camps it appears always to have been cooked. The recent demonstration that fresh yeast (166) in the diet leads to rapid depletion of thiamin also appears to have little direct relationship to the clinical states observed here, but warns of probable further complications in the absorption and utilization of vitamins. Similarly the anti-biotin factor (avidin) in raw egg-white (97) is heat labile. The food of prisoners-of-war appears to have been sufficiently cooked to avoid such factors.

V. GENERAL DISCUSSION

The neurological disorders found in prisoners-of-war in the Far East are found to have been well known in various tropical countries, and without doubt occur in more temperate climates also. There is universal agreement that these disorders are related to dietary defect, though their relationship to each other and the precise kind of dietary defect remains in doubt. From our own observations and from a review of reports of such cases it is clear that several distinct

syndromes besides the distal polyneuritis of beriberi may make separate and independent appearance. These are:

1. Retrobulbar neuritis
2. Spinal ataxia
3. Spastic paraplegia
4. Burning feet ("Aerodynia") with corneal changes
5. Deafness
6. A myasthenic bulbar syndrome ("Kubisagari").

There was some evidence of an independent vestibular syndrome (the "camp dizziness" of Batavia), but we had no personal experience of this. Aphonia has an uncertain independence of the polyneuritis of beriberi.

There may still be uncertainty in the minds of some as to the relationship of polyneuritis to thiamin deficiency. In such case the distal polyneuritis of beriberi should be added as yet a seventh independent unknown.

1. Inter-relationship of the Disorders

Most, if not all these conditions have been described in association with beriberi, but the statements of our own patients and a critical review of the reports of others indicates that such association has been fortuitous. The evidence that retrobulbar neuritis is a complication of beriberi is chiefly in Japanese writings but careful examination of the detailed report in English made by Kagawa (115) led to the conclusion that the condition is an independent entity, even less complicated by beriberi than might have been expected in view of the habitual diets in Japanese cities. The relationship of spinal ataxia to beriberi and to retrobulbar neuritis is more difficult to define. Much confusion has been caused by the acceptance by some of absent tendon jerks and incoordination as evidence of polyneuritis and hence of beriberi.

The disorder described by Scott (196) in sugar plantation workers in Jamaica in 1918 has an exact parallel in that found by Pallister (173) in the Chinese population in Malaya. In neither group was beriberi present and in both a spinal sensory type of ataxia, with absent tendon jerks and loss of kinesthetic sense was accompanied by retrobulbar neuritis in one fifth to one third of the cases. In these two instances the ataxia was the prominent feature. In the "prison disease" of Landor and Pallister (126) in Singapore the tendon jerks were not lost but the condition was otherwise similar. Angular stomatitis and scrotal dermatitis were prominent in all these outbreaks. The disorder described by Moore (158) in Nigeria and Metivier (150) in Trinidad differed in that retrobulbar neuritis was the common symptom and ataxia occurred only in a small proportion of cases. The retrobulbar neuritis, with bilateral central scotomas, temporal pallor of the discs, and seldom if ever progressing to blindness or loss of pupillary reaction to light, appears to be identical in all these groups. The differing proportion of ataxia indicates independent origins, but close relationship between the two disorders.

There is therefore good evidence that both retrobulbar neuritis and spinal ataxia are independent of beriberi and to a lesser extent of each other, and our

own experience entirely bears this out for each was found to have occurred in considerable severity without the other in Eastern prison camps. The relationship of deafness to these syndromes is obscure but is consistent with its being directly associated with spinal ataxia of sufficient degree, for in our own series it was found only in the presence of severe disability. Here it was not associated with vertigo, and like the retrobulbar neuritis, did not lead to complete loss of function. The "camp dizziness" described in Batavian camps appears to have occurred independently of the other nervous disorders, and initial vestibular disturbance here indicates a closer relationship to the vertigo of pellagra (probably a labyrinthine neuronal degeneration). To this extent, then, disorder of the 8th nerve may stand alone and have an independent pathology. Aphonia was an extremely infrequent symptom in the groups examined by us and we are not able to deny the possibility of a previous attack of beriberi in these patients, having questioned only 3 of them on this point. In view of the onset of aphonia at a later date than the beriberi in our case 13, the occurrence of "dysarthria" in the similar cases of ataxia reported by Scott (196) in Jamaica where beriberi was absent, and the occasional examples of aphonia in relation to ataxia reported by others (216) (52) lead us to believe that a type of vagal paralysis independent of beriberi is related to the ataxic syndrome.

Some have considered the ataxia a type of polyneuritis. Affection of the dorsal root ganglion can certainly account for a disorder of sensation that is predominantly of proprioceptive kind, associated with loss of tendon jerks, for the disease called "infective polyneuritis" commonly achieves this, and scattered inflammatory changes in the ganglia and nerve roots are then found. The "spinal ataxia" of nutritional deprivation has a very different course from that of infective polyneuritis, but such cases as have lost the tendon jerks could have primary ganglionic degeneration, if the dissociation of sensation were explained by affection of chiefly the largest nerve cells. Pains closely resembling lightning pains were a feature of some cases, suggesting disease of dorsal root ganglion cells, but this was a rare feature. The absence of motor weakness and wasting certainly differentiates these cases from distal types of polyneuritis including beriberi. The cases where the tendon jerks were retained cannot be explained in this way, and must have degeneration of the dorsal columns of the spinal cord. If, as we found in our own cases, some retained the tendon jerks and some did not, and, as others have noted (196) (173) the tendon jerks are at first increased and later lost, the presumption is that damage to the thoracic or cervical portion of Goll's tract in the dorsal columns is primary, without ganglionic changes, and extended to the lumbar portion of the cord. If this is in fact proven by autopsy, for which there is yet only the unsatisfactory Marchi material of Scott (196), the "spinal ataxia" of human cases is different from the dorsal root ataxia in pantothenic acid and pyridoxine deficiency in swine (268) (265) (267) or any other known experimental deficiency except possibly pantothenic acid defect in chicks (179). The relationship of the "spinal ataxic" syndrome to the pellagrous conditions of stomatitis and scrotal dermatitis, and the description of similar ataxia with loss of deep sensibility in

pellagra make it indeed likely that it is the dorsal column disease of pellagra originally described by Belmondo (19).

The state of chronic simple spastic paraplegia found in 9 cases observed by us formed a striking contrast to the remainder of the series. Transitional spastic-ataxia cases were few in number. In some the onset of the spastic condition had included a severe cerebral illness with diplopia, mental confusion and a liability to epilepsy. The possibility that this initial state was either Wernicke's polioencephalitic syndrome or the less clearly defined confused, disoriented states seen in pellagra has to be considered. Though the cerebral lesions may be extensive (40) Wernicke's polioencephalitis is not associated with spastic residual disorder, and nystagmus is prominent in the acute state. The characteristic hemorrhagic change was absent at autopsy in Singapore cases. The response of mental changes in pellagra to nicotinic acid (213) and the finding that certain states of confusion, with rigidities and reflex sucking and grasping, in elderly patients without pellagra also respond to nicotinic acid (53) (113) (234) suggest an alternative possibility. The patients in Singapore did not respond to small dosages of nicotinic acid. The rigidities in the cases of "nicotinic acid encephalopathy" clear up rapidly and completely with treatment. Mental confusion is a non-specific state, and the only distinctive features of the Singapore cases, early diplopia, absence of hallucinations, liability to epilepsy and residual spasticity, are unlike any known encephalopathy.

The majority of spastic cases seen in Singapore and also of those seen by us had no such initial encephalopathy. There was no question of amyotrophic lateral sclerosis for fibrillation and atrophy were absent. Inflammatory or compressive disease of the spinal cord was excluded by examination of the spinal fluid both in early and late stages. The question of the nutritional spasticity of lathyrism therefore arises. No lathyrus pea had been consumed, but the evidence that this pea, or the vetch, *Vicia sativa*, has some exclusively toxic action is conflicting and unconvincing. There is no doubt that *Lathyrus*, and at times *Vicia* is associated in some way with the production of spasticity but the data strongly suggest that these act by facilitating a type of breakdown which can occur as a result of malnutrition alone. Damage limited to anterolateral tracts in the spinal cord can occur in pellagra as a rare complication (242) (128). On the other hand the dorsal columns, as well as the anterolateral tracts, may be damaged in lathyrism (38), with corresponding loss of sensation (12) (182) (200). The encephalopathic illness in some cases is in favor of a cerebral pathology, but in at least one naked-eye autopsy at Singapore (260) the spinal cord was found to be studded with small areas of degeneration. From our own examination of recovered cases we concluded not only that both a spinal and a cerebrospinal form of the spastic syndrome had occurred, but that combinations of the spastic spinal disease with the ataxic spinal disorder were more common than the recorded cases in the literature indicate. Finally, all of these variants were commonly associated with retrobulbar neuritis at the time of onset, though each had occurred independently in isolated cases.

The conclusion that "nutritional ataxia" is a spinal cord disease, occasionally

associated with damage to anterolateral tracts, immediately raises the question of its relationship to subacute combined degeneration (combined system disease). The resemblance was recognized by Landor and Pallister (126). The severe loss of sense of vibration in relation to loss of postural sensibility is characteristic of combined system disease. Mild impairment of sensation to pinprick and touch below the knee, extensive paresthesias of numbness and tingling, and late loss of tendon jerks also occur. These have been attributed by some to a coincident neuritis, but we have found no loss of fibers in the peripheral nerves in two cases exhibiting these phenomena, and in 4 cases Greenfield and Carmichael (92) found only an impoverishment of myelin in the nerves of the feet, without Wallerian degeneration. Cohen (54) and Turner (243) have observed optic atrophy, and, in combination with the cerebral lesions of combined system disease Bickel (21), Woltman (273), Adams and Kubik (3) and others have found lesions of the optic chiasm. Against these strong points of resemblance between the two conditions are some equally strong objections to their absolute identity. First, pernicious anemia is obligatory in combined system disease whereas it has been consistently absent, not only in the chronic nutritional ataxias but even in the acute and fatal cases of Scott (196) where only a mild hypochromic anemia was found. Retrobulbar neuritis is an excessively rare complication of combined system disease, whereas it has been common in the nutritional syndrome. Turner (243) found a centro-cecal scotoma, Bickel (21) a truly central scotoma in combined system disease. We ourselves have often looked for visual defect but in vain. The cases in which patchy degeneration of myelin in the chiasm have been found at autopsy (273) (3) had not complained of, or shown, visual disorder, and had a severe terminal mental derangement. The visual disturbances in prisoners-of-war had in contrast presented themselves early in the illness, with clear-cut signs, and without evidence of cerebral involvement except in a few of the cases of "spastic encephalopathy." These latter however were of the purely spastic type, without dorsal column lesion. Finally, though the dorsal columns are affected first in combined system disease, the appearance of bilateral extensor plantar responses is inevitable beyond a certain degree of severity. In nutritional ataxia extensor plantar responses were a rarity. We therefore conclude that the retrobulbar neuritis-ataxia-spasticity syndrome is not combined system disease. The order of difference chiefly concerns accentuation within the nervous system, and is such that breakdown of parts of the same metabolic mechanism may account for the two disorders, but results in two different ways, one of which is associated with pernicious anemia.

Although the cause is equally obscure, a disease that raises precisely the same questions has been described by Schob (193), Scherer (190), Davison (61) and others in monkeys and apes after long confinement in captivity ("cage paralysis"). There is also no anemia, and the incidence of the disease varies, having at times a predominantly cerebral pathology, at times spinal, with consistent damage to the chiasm and optic nerves. Very numerous small areas of demyelination appear in the white matter of the cerebral hemispheres and the

optic chiasm. In the spinal cord these areas extend to become confluent and produce an appearance identical with that of combined system disease. The dorsal columns may be alone involved (193). There is no evidence of inflammatory disease and grey matter is not affected. There may be a long remission after an initial illness, with subsequent appearance of a fresh crop of patches (190). In the optic tracts and chiasm the areas of demyelination are small (61). Such a pathology could well explain the curious fragmentation of the scotoma sometimes observed in nutritional amblyopia during recovery, and exemplified by our case 4 (fig. 2). Further it would explain the interrelationship between nutritional retrobulbar neuritis, spinal ataxia, spastic ataxia, and spastic encephalopathy, with varied accentuation and pure syndromes. The description of small areas of demyelination seen in the white matter of the hemispheres in fatal cases of spastic encephalitis in Singapore is recalled. In Schob's original case (193) there was also degeneration of dorsal nerve roots, but the pathology of the disease in the light of subsequent reports has been purely central. Root degeneration must therefore represent some coincident disorder. The brain stem is sometimes affected (190) but whether diplopia, deafness, or dysarthria can come about in this way has yet to be determined. The disease of Schob and Scherer has no resemblance to any pathology reported in experimental deficiencies of known factors and no particular glossal or cutaneous affection is described in association with it. It has no close resemblance to multiple sclerosis, and the sparing of grey matter differentiates it from demyelinating encephalomyelitis.

Our first conclusion was that both nutritional amblyopia and the nutritional spinal syndromes were related in some way to pellagra. None of the deficiencies of known members of the vitamin B complex, shown to be responsible for the various mucocutaneous disorders of pellagra, has yet been proven to account for the nervous symptomatology. On the other hand the spinal cord lesion of pellagra has often a close resemblance to combined system disease (261) both in its distribution and in its vacuolated appearance. In other cases there has been a diffuse affection of individual nerve fibers in the dorsal and lateral columns (7) (93). This last type is consistent with the results of degeneration of isolated nerve cells, as part of the widespread neuronal degeneration that is characteristic of classical pellagra. Pentshew (178) drew attention to both types of change and concluded that both patchy degeneration of myelin and cell changes resulted from the hyaline degeneration of capillaries that Winkelman (263) and others had noted. The small areas of vacuolated demyelination in pellagra, combined system disease, and Schob-Scherer disease are certainly related each to a small venule on first appearance. We are of the opinion that both types of change belong to pellagra, but are independent, for the nutritional disorders in prisoners-of-war in Malaya and Burma failed to produce the diffuse mild spastic change with muscular fasciculation and mental confusion that we associate with cell disease. Instead the hitherto little known spinal and cerebral demyelinating type emerged in pure forms resembling combined system disease. It is evident that these questions can only be finally settled when detailed histo-

pathological studies are available. It is hoped that further studies of the neuropathology of pellagra will also be stimulated in view of the evidence presented here.

The condition of "burning feet" deserves wider recognition. It too is related to pellagra. It has long been known in India and the type of affection occurring in Malaya and Singapore was evidently of the Indian and Burmese type described by Grierson, Malcolmson and others, where the disorder is largely or completely subjective and confined to the feet. Its relationship to the Philippine "lapnus" (68), where accompanying scaling redness and peeling give more close resemblance to the acrodynia of children, and to the Ceylonese type beginning with burning in the hands, is obscure. These conditions may well be pyridoxine deficiency. The condition as seen by us was closely related to granular corneal degeneration and less closely to "spinal ataxia," and corresponded with the description of Metivier (150) and Sharples (202). In Singapore camps it occurred in a relatively pure form. Major Graves informed the writer that a patient who had had one leg amputated developed subsequently a burning in both feet, a possible indication of central nervous pathology. The relationship of the burning sensation to temperature, the lack of neurological signs except in late stages, and the relief obtained from niacin all suggest a vasomotor pathology. When alterations in reflexes develop they may be either exaggeration or loss, spasticity or ataxia, suggesting that a stage of deficiency has been reached where multiple breakdown in enzymic function (classical pellagra) is liable to occur.

The myasthenic bulbar condition encountered at Singapore and Carbanatuan (Luzon) form a sixth and distinctive variant of the disorders described. The circumstances of its occurrence merit its inclusion in this discussion, for not only was evidence of inflammatory origin inconstant, but the description of identical outbreaks in Japan (154) and Switzerland (83) in peasant populations gives additional reason to suspect dietetic fault. In Singapore the diet was unbalanced by an undue amount of *tapioca flour*, and on Luzon the Philippine *cassawa* formed a large part of the diet at the time. If there was some doubt as to the part played by a previous attack of dengue, or of ingestion of the bitter cyanic outer bark of cassawa on Luzon the Singapore experience indicates that it is the poverty in some essential (probably tryptophane) shared by tapioca flour and cassawa (from which tapioca is made) that is the important factor. It should be emphasized that the benign course of the condition differentiates its causation from myasthenia gravis, though otherwise it is almost certainly a disorder of neuromuscular transmission of identical kind.

2. Course

Two remarkable features of these disorders are their relative suddenness of onset after long latency and their limitation in degree. It might have been expected, and indeed is so described in the general textbooks, that the pathology of a deficiency disease leads to slowly progressive disorder of function and structure, commensurate with the cumulative biochemical defect. Even in beriberi

the sudden appearance of extreme weakness as well as sudden death, has been commented upon by many authors. The decompensation of unsuspected cardiac disorder has naturally been held to account and perhaps has been responsible for causing the limitation of metabolism and hence of the disease, to weakness and wasting below the knee and elbow. Both features may nevertheless occur when cardiac features are minimal or absent. Burning feet and aerodynia are the only varieties of disorder where the course is consistently one of steady progression unless the dietary habits are altered.

On the other hand the neurological symptoms were not of such sudden or immediate onset as may be expected of vascular lesions. A subacute progression over 1 to 3 days was the most rapid in our series.

The limitation in degree was most clearly seen in relation to "nutritional amblyopia" or "nutritional deafness" which do not appear to progress to complete blindness or deafness respectively. Spinal ataxia though severe in some cases involved the upper limbs little if at all. None of our spastic cases, and those in the reports of lathyrism in the literature, had progressed to complete paralysis of the lower limbs. In all of these the development of severe disability overnight is commonly related.

The long duration of privation in the prison camps surely gave every opportunity for these disorders to continue development to maximal degree, for in spite of the best treatment available, many must have continued the basic deficiency for long periods after developing symptoms. A very large number succumbed to beriberi and possibly many of the worst cases of spinal ataxia died of an illness that was thought to be beriberi. The series of cases reported by Scott in 1918 was the most acute and severe on record, yet fatal termination was in the nature of a sudden collapse after 2 or 3 days of acute diarrhoea. No encephalopathic or quadriplegic form was described. Progression to a generalized cerebral illness occurred only in the "spastic syndrome" where some patients succumbed to a cerebral illness in the early stages of the disease.

In relation to the suddenness of appearance of symptoms and their relatively stationary or remitting course thereafter the possible relationship of attacks of dysentery or fever must be considered. It was common to find that after months of improvement in symptoms an attack of dysentery or fever would lead to relapse, and isolated cases described an onset during or shortly after such a transient disorder of metabolism. The great majority of patients could not relate the onset of their symptoms to any transient general disorder, and this also is supported by the statements of medical officers of prison camps.

The sudden development of extreme disorder after long latency is described in riboflavin and pantothenic acid deficiencies in animals, particularly in severe degrees of deprivation, but also is a first sign in chronic states. Wintrobe and his associates (265) noted that some ataxic swine reached a stationary stage, and some improved after an initial attack, even though maintained on the defective diet. It has been shown (120) that black tongue appears in dogs when the two co-enzymes of niacin fall to a critical value. Gradual attenuation to zero level is not necessary. The peculiar course of the neurological nutritional

syndromes indicates the presence of some similar "critical threshold" in the mechanism of their causation.

3. *Causation*

The estimation of the adequacy of a diet is a notoriously difficult procedure, for even if all the constituents are accurately known the proportional loss in preparation, cooking and distribution, and the amount not eaten or ill-digested may be decisive. The diet of a Malayan prison where beriberi had constantly occurred was stated by Wright to be "correct and liberal" but was found by Cowgill (57) to be "borderline in its adequacy." The same suspicion was held of Brazilian diets associated with the development of beriberi. The diet of the prisoners described by Spillane and Scott (216) appears to be fully adequate in all respects, but the cooking was "far from ideal." Pallister (173) has noted that Malays, Chinese and Indians, in a Malayan civil prison, eating parboiled rice with a moderate subsidiary diet, developed the ataxia and retrobulbar neuritis he called "prison disease," whereas Indian laborers on an almost identical diet developed the syndrome here described as "burning feet" sometimes with ataxia. The subtle differences which must be held to account are yet to be elicited. The present review indicates however that the different kinds of specialized nervous disorders are much more numerous than has hitherto been believed and represent correspondingly more numerous mechanisms of causation. These may be discussed in a general way.

It is inevitable that some poisonous alkaloid in one or more of the articles of food should be held to be a probable cause by some. The history of investigations of lathyrism has been punctuated by claims for the existence of such a poison in *Lathyrus*, or *Vicia*. Claims for extraction of a toxin from maize, causative of pellagra, were made in the last century (105) (131). It is by no means clear that ergot of rye always leads to ergotism. That pellagra should occur with diets of maize, which is relatively rich in riboflavin and niacin, and be infrequent on diets of either whole, parboiled or milled rice which is poor in these substances has been discussed by many writers (16). It was at first suggested that some substance in yeast and liver detoxicated the specific agent in maize (46) in the prevention of pellagra by these substances.

The question of toxicity, however, is relative. Views as to the nature of action of poisons are undergoing radical change. The recent demonstration that physostigmine, for example, acts by providing an alternative substrate for cholinesterase (55) and thus "poisons" the action of the enzyme, indicates the close relationship between the points of action of poisons and of accessory food factors. Nevertheless there are distinctive features of the disorders known to be related to consumption of plants containing alkaloids. The symptoms are immediate and are cumulative. An excellent example is the description given by Brinton (32) of an outbreak of a nervous disorder in the nature of tremors and ataxia progressing to coma, caused by the contamination of Abyssinian wheat by the seeds of the flax darnel (*Lolium temulentum*). This type of intoxication was described by the poet Ovid (109). It is not so much the nature of the disorder

as its immediate and progressive course, which is altogether different from that of the neurological disorders discussed here. The same may be said of the action of helladonna, hashish, morphine or indeed of all alkaloids. The vegetable poisons which produce degenerative nervous lesions, such as apiol which leads to a painful peripheral neuritis, and quinine which may damage the optic nerve, also exert a direct, immediate and cumulative effect, and appear to require some idiosyncrasy. As to contaminant substances, whether mould or plant, it should be clear that such an intoxication derived from sugar cane, as hypothesized by Scott in Jamaica is unlikely to be developed by cassawa in West Africa and rice in Malaya.

The relative infrequency of neurological disorders reported from prison and concentration camps in Germany is remarkable in relation to the low calorie diets there consumed. I have questioned medical officers who assisted in the relief of Belsen and other camps and found none who had observed the conditions found in Burma, Malaya and Batavia.[2] Sheer starvation has always been regarded as less damaging than a high carbohydrate diet with inadequate vitamin coverage, but the biological value of the protein consumed is also of great importance. Goldberger and Tanner (85) discussed the rarity of pellagra in Germany in the 1914–18 war and considered the type of protein the decisive factor. They observed the beneficial effect of treatment of pellagrins with cystine or tryptophane. In their later work (86, 87) these investigators demonstrated the lack of PP factor in relation to the occurrence of pellagra, but insisted that a faulty protein (amino-acid) component in the diet was able to modify the outcome. Though it has been realized for many years that certain amino-acids were essential for growth and health (136) the factors underlying this necessity have remained obscure until quite recently. The demonstration that nicotinic acid (88) and riboflavin (197) (235) could correct the essential mucocutaneous lesions of pellagra, left the part played in causation of maize corn, itself relatively rich in these substances, in doubt. Handler (99) concluded that corn meal *per se* could be a factor in production of black tongue, and Krehl and his associates (123) proceeded to show that corn increased the bodily requirement of nicotinic acid, whereas milk decreased it. Casein protected against the harmful effect of corn grits (124) and l-tryptophane at a 0.4 per cent level produced a dramatic relief of black tongue produced by corn grits. This effect of casein and its contained tryptophane was attributed to an extensive change in the intestinal flora in favor of natural synthesis of nicotinic acid in the alimentary canal. The only clear example of such a mechanism in prison camps was an unexpected outcome of unbalancing the diet with cassawa or tapioca. The result was not niacin or riboflavin deficiency as ordinarily recognized but a myasthenic bulbar syndrome with the characteristic failure of muscular contraction after repeated use. Such a situation is however complicated by additional factors, for it now appears that an established deficiency in nicotinic

[2] Description of the effects of starvation in German prison camps without neurological complications, have now appeared (Mollinson P. L., Brit. Med. J., 1: 4–8, 1946 and Leyton G. B., "Effects of Slow Starvation," Lancet, 2: 73–79, 1946.).

acid in some way thwarts the beneficial action of certain proteins such as soy bean and egg albumen (122). Established deficiency in pyridoxine results in a disorder of metabolism of tryptophane with the production of xanthurenic acid (14). Thus multiple deficiencies may result in severe disorder of protein metabolism whose effects remain to be defined.

Clark (49) pointed out that cassawa bears the same relationship to pellagra in West Africa and Ceylon as maize corn in other countries. Without citing direct evidence he pointed to the presence of cyanic substances, mandelic nitrite in maize and a cyanogenetic glucoside in cassawa, as probable inhibitors of riboflavin (50) and nicotinic acid (51). He also considered (50) that the beneficial effect of cobalt in preventing "coast disease" (anemia) in sheep in Australia may be attributed to the formation of insoluble cobalt-cyanide with the cyanic clover in the pasturage of the areas concerned. The similar ataxia of sheep in Australia reported to be curable by traces of copper (143) may have similar explanation, *for neither cobalt nor copper appear to be essential to the living* organism. Though the proof of the inhibitory effect of such cyanic substances does not appear to be complete, this possibility and the far reaching importance of lack of tryptophane, the anti-vitamin effects of certain raw fish, raw egg white and fresh yeast all indicate that the content of any given diet in known vitamins is far from an accurate indication of the mechanism of nutritional lesions. The diets in the prison camps certainly provided a high carbohydrate content with low values for all the vitamin B complex, and in addition proteins of poor biological value. That animal protein is not *per se* essential though it can eke out the defects of other inadequate protein, is shown by the absence of deterioration of health of adults in the Channel Islands, during the German occupation, who subsisted chiefly on whole meal bread and fresh vegetables (125). The diets in prison camps in the East were severely defective in fresh vegetables.

Experimental studies in animals have indicated riboflavin, pyridoxine and pantothenic acid as the known vitamin substances of which deficiency is most likely to lead to degeneration of the spinal cord and certain afferent neurones. Such studies suffer from the difficulties introduced by differences in species and natural diets, and from inability to protect against interactions with deficiencies in factors as yet unknown. There is as yet no clear indication that deficiencies in these substances is responsible for retrobulbar neuritis, deafness, ataxia, spasticity or the myasthenic syndrome. If degeneration of the cochlear mechanism is related to riboflavine deficiency (56) it remains to be explained how this may be caused in isolated form. If riboflavine deficiency were the cause of spinal ataxia with deafness the absence of mucocutaneous signs of riboflavine deficiency in most of our own cases and those of Metivier is an added difficulty. The ataxic paraplegia of swine, traced to deficiency in pantothenic acid by Wintrobe and his associates has a superficial resemblance to the ataxic disorders we have described in man, yet the disease in swine is a ganglionic degeneration; that in man indicates intramedullary lesion. Further, though deficiency in the closely related substance pyridoxine is related to a disorder resembling acrodynia in every particular, "burning feet" without cutaneous lesion requires further explanation. It would appear that some defect, closely allied to pan-

tothenic acid deficiency is related to the appearance of spastic paralysis, but this has been described only in chicks, and gives suspicion of a further unknown factor. It is evident that no known experimental deficiency accounts for the neurological syndromes observed.

Evidence of causation derived from the effects of various agents used in treatment are conflicting. Even in rigidly controlled animal experiment deficiencies now known to be due to pyridoxine lack were earlier reported to be relieved by the administration of riboflavin. Stomatitis due to riboflavin deficiency improves slowly in response to niacin. Though relief of retrobulbar neuritis by administration of crude extract of rice polishings (115) or by riboflavin (150) (258) has been reported, if given in the early stages, or encouraging results found from giving riboflavine (259) (4), or from yeast extract (159); these have not been confirmed by others (173) (216) (52) by Batavian medical officers or by ourselves. It is difficult to exclude the effect of coincident return to full diet in clinical trials, as Sinclair (209) has emphasized. Though nicotinic acid was found to be successful in combating "burning feet" in Singapore camps and also in Hong-Kong (52) the effect may have been indirect and related only to the vasodilating effect of this agent. Recent work on tryptophane has shown that the diet is as important as the vitamin.

Disorders that are as destructive of vital and irreplaceable nervous tissue as these are more amenable to prevention than cure. The effects of the prophylactic use of "food yeast" to the extent of 10 gm. daily, and the cultivation of strains of *Torulopsis utilis* with high yields of B complex, at present being extensively tried out in Nigeria (104) will be watched with interest. Distribution of powdered yeast by the Red Cross in the southern United States from 1927 to 1934 certainly reduced the incidence of more usual types of pellagra (discussion of paper by Spies *et al.*, 213).

Whatever the actual mechanism of deficiency or neutralization of specific essential food factors resulting in the appearance of these various neurological, neuromuscular and vasomotor disorders there nevertheless remains the fundamental question of *localization of effect.* Whereas the material here presented gives little indication that the defective agents are known vitamins it clearly indicates that the resulting disorders are highly specific. It is difficult to account for such localization except by the postulation of some specific unknown metabolic factor or enzyme essential for the adequate performance of each susceptible function.

It is of interest that though all these neurological conditions related to prolonged dietary defect may occur in temperate climates, and though some of them closely resemble disorders such as combined system disease, there was no evidence that any of the well known degenerative nervous diseases, such as multiple sclerosis or amyotrophic lateral sclerosis was caused by the dietary defects experienced in prison camps in South East Asia.

VI. CONCLUSIONS

A series of independent neurological disorders related to dietary restriction has been observed in released prisoners-of-war. Except for the usual polyneu-

ritis of beriberi, and possibly an obscure myasthenic syndrome brought about by unbalancing an already precarious diet by ingestion of cassava or tapioca, the neurological disorders were not related to beriberi. A condition of "burning feet" allied to acrodynia was clearly part of the syndrome of pellagra and could occur independently. Retrobulbar neuritis, spinal ataxia, spastic ataxia, and simple spastic paraplegia occurred in various combinations and separately. It is concluded that these also represent isolated occurrence of various neurological manifestations of pellagra. The conditions associated with experimental production of known deficiencies do not account for the disorders observed. The only comparable condition is "cage paralysis" of monkeys. The disorders are highly specific in the localization of effect to different parts of the nervous system and indicate the presence of correspondingly specific, but unknown processes of abnormal metabolism. The manner in which the nervous system is damaged is reminiscent of the subacute combined degeneration of pernicious anemia, but the accentuation was different and anemia absent. Detailed neuropathological studies are badly needed.

There is as yet no indication for the use of any of the pure vitamin substances in treatment of any of these affections. Crude extracts of yeast and liver have given good results in mild or early cases, and as source of both known and undefined factors in the vitamin B complex, are the therapeutic agents of choice. Eggs have been recommended by some, and also have value as a crude source of B complex. A balanced protein intake is as necessary as a vitamin supplement. As in the prevention of pellagra the provision of fresh vegetables in the diet would appear of first importance as a prophylactic measure.

VII. APPENDIX

Abstract of Specimen Histories

Case 1. Pte. J. G., age 30, released from Rangoon jail in May, 1945, after two years of imprisonment. The first symptoms began after a year of captivity and consisted of shooting pains in the legs associated with unsteadiness, paresthesiae and numbness spreading from the feet to involve the thighs in several months. Failing vision and deafness had been first noticed only after the onset of the pains. The onset of symptoms occurred after seven months of a diet of parboiled rice three times a day, cooked vegetables (potatoes, Burmese cabbage, pumpkins and marrows) about twice a week and a small quantity of cooked meat (buffalo, beef, pork) once a week. Tea without milk or sugar was allowed. Adequate salt as given. There was never any bread, butter, fat, milk, fruit or fresh vegetables. Several months after its onset the condition became stationary. Walking, vision and hearing remained unchanged and pains ceased.

On examination: visual acuity was 6/60 R and L with bilateral central scotoma (fig. 1) and temporal pallor of both optic discs. Pupillary reaction to light was ill sustained, to accommodation brisk. There was bilateral nerve deafness of moderate degree. No weakness or wasting was found in upper or lower limbs, but there was moderate ataxia in walking and staggering on turning. Rombergism was present. There was hypalgesia below the midthigh on both sides, with indefinite border. Position sense was lost in the toes and ankles, vibration sense lost in the toes and lessened at the knees. The knee jerks were brisk and equal and ankle jerks brisk and equal. Plantar responses both flexor. The cerebrospinal fluid pressure and contents were normal, Wassermann negative, and blood Wassermann reaction negative. Rbc 4,640,000 per cmm.; Hb. 95 per cent; MCV

91.3, Wbc 17,000 per cmm.; Eosinophils 8 per cent. BT malaria parasites present. Stools contained hookworm ova. Gastric test meal, free acid in second sample. X-ray examination of the spinal column and skull failed to show any abnormality of bony structure.

Neurological Diagnosis: Nutritional retrobulbar nauritis and ataxic syndrome.

Case 2. Pte. J. P., age 27, taken prisoner on 24.2.42, and captive in Rangoon jail. Numbness of the feet and unsteadiness in walking began 8 months later. Visual failure and deafness began a few days after the onset of unsteadiness. All symptoms increased rapidly in severity for 9 days then remained stationary. The diet had been identical with that of case 1.

On examination: he showed a marked mental apathy with paranoid behavior. Visual acuity was 6/60 R and L with bilateral small central scotoma and temporal pallor of both discs. Reaction to light was poor in both pupils, but good to accommodation. There was bilateral mild nerve deafness. There was extreme ataxia of the lower limbs and gross Rombergism. Gait was impossible without assistance. The limbs were hypotonic and muscular strength was only moderate in all movements, but was as good in dorsiflexion of the ankle as elsewhere. There was hypalgesia of the legs below the knees, but not of the feet. Postural sense was lost in the toes only, but vibration sense was completely absent in both lower limbs. The knee jerks were present but diminished, the ankle jerks absent. Both plantar responses were extensor. The cerebrospinal fluid was normal in pressure and contents, with negative Wassermann reaction. Blood W.R. negative. Blood count: Rbc 4,530,000 per cmm., Hb. 100 per cent, MCV 97.8, Wbc 13,000, Eosinophils 11 per cent. Gastric test meal free acid in sixth sample. X-ray of skull and spine negative.

Neurological Diagnosis: Nutritional retrobulbar neuritis with spinal ataxia and deafness.

Case 3. Sgt. D. G., age 28, transferred to Rangoon jail on 19.5.42, had developed shooting pains in his feet and knees 9 months after capture. Numbness and paresthesiae of the feet began a few weeks later, followed by similar symptoms in the hands, then ears and nose. His gait became unsteady and was worst a year after imprisonment, since when it had steadily improved with temporary set backs each time he had suffered from fever. Blurring of vision in reading developed in July, 1943, and at his worst he was unable to recognize people. There was no history of deafness. The diet had been similar to that of cases and 1 and 2 but with the occasional addition of fish cooked in cooking oil, or an egg, or raw cucumber, and in the third year of some fresh vegetables.

On examination on release: visual acuity was 6/36 R, 6/24 L with a very small central scotoma R, nil L. Both discs were very pale with choroidal crescent. The pupillary reactions were normal, there was no deafness or other cranial nervo disorder. Gait was normal, but there was slightly positive Romberg's sign. No muscular weakness or atrophy was demonstrable in any part. There was no impairment of sensation to touch or pinprick. Postural sense was impaired in the toes, but not lost. Vibration sense was completely absent in both lower limbs, iliac crests and lumbar spine. Both knee jerks were brisk and equal, the ankle jerks absent. The right plantar response was flexor, the left doubtful. The cerebrospinal fluid was normal in pressure and contents, Wassermann negative. Blood Wassermann negative. Blood count: Rbc 3,940,000 per cmm., Hb. 85 per cent. Color Index 1.09, MCV 92.3, Wbc 15,600 per cmm., Eosinophils 7 per cent. Gastric analysis, free acid present. Stools: hookworm ova present. X-rays of skull and spine negative.

Neurological Diagnosis: Nutritional retrobulbar neuritis and spinal ataxia.

Case 4. Fus J. W., age 30 captured on 24.4.42 and in Rangoon jail for 3 years. Difficulty in reading began 15 months after capture, and after 3 weeks he could read only the largest print. Vision stationary since. The diet had been essentially that of case 3.

On examination on release: visual acuity was 6/36 R and L with bilateral small scotomas grouped round the fixation point (fig. 2) and temporal pallor of the optic discs. The pupil-

lary reactions were brisk. There was no deafness and other cranial nerve function was normal. Motor power was excellent, there was no loss of sensation, the knee jerks and ankle jerks were all naturally brisk and equal. The plantar responses were equivocal, but the gait was normal and there was no evidence of spasticity or ataxia. The spinal fluid was normal, the Wassermann reaction negative in fluid and blood. Blood count: Rbc 5,900,000 per cm., Hb. 120 per cent, C.I. 1.01, MCV 84.7, Wbc 8,000, no abnormality on differential count. Gastric analysis showed free acid present. Examination of stools disclosed no abnormality.

Neurological Diagnosis: Nutritional retrobulbar neuritis.

Case 5. Sepoy B in Singapore Camp from February 1942 found his vision poor for small objects in June 1943 and soon after this developed unsteadiness in walking. He had remained "much the same" since then.

On examination in September 1945 he had a slight visual loss (central scotoma) with pallor of temporal sectors of the discs. He was extremely ataxic in gait, but could walk with the aid of a staff (fig. 6). Motor power and muscular bulk were unaffected, except that dorsiflexion of the ankles could be easily overcome by the examiner. K. J. both absent, A. J. both absent, plantar responses flexor. Pin prick was blunted over the dorsum of the feet and light touch impaired below the knees. Position sense was impaired in the toes and vibration sense completely lost below the iliac crests. Calves slightly tender.

Neurological Diagnosis: Nutritional retrobulbar neuritis, spinal ataxia, with some evidence of mild peripheral neuritis.

Case 6. Pte R. F. Imprisoned in Singapore February 1942 developed difficulty in reading and in recognition of small objects in January 1943. Vision rapidly worsened but subsequently improved slightly with treatment and remained stationary. Unsteadiness in walking developed in February 1945 but improved rapidly on release. On examination in September 1945 he was found to walk well except that he lifted his feet irregularly, often too high and walked on a broad base. The optic discs both showed temporal pallor. Muscular development and power was normal with no weakness of dorsiflexion of ankles. No tenderness was found. The knee jerks were present but sluggish, the ankle jerks both brisk. Plantars flexor. Position sense was defective in the toes, vibration sense absent.

Neurological Diagnosis: Nutritional retrobulbar neuritis with spinal ataxia.

Case 7. L/Cpl. A. W. Captured in Singapore February 1942. After some months was given work in a stone quarry, on a diet consisting of a cupful of rice, a small helping of meat, with sweet potatoes. In May 1942 dimness of vision commenced and after 3 weeks was so bad that he could not recognize faces. He then became forgetful. A month after the onset his arms and legs began to become weak, he stammered and spoke slowly. He became mentally confused and remembers little of following months except that he lost sphincter control. He suffered from attacks of unconsciousness. By May 1943 he was recovering slowly in camp hospital on a special diet of eggs and yeast extract. He continued to recover gradually until December 1944, stationary since. There was no history of malaria or dysentery. On examination (September 1945) vision was still poor for small print, the discs showed temporal pallor. There was no other defect in the cranial nerves or upper limbs. Both lower limbs were extremely spastic in extension with very brisk knee and ankle jerks and clonus, and bilateral plantar responses. No loss of sensation of any kind could be demonstrated. The gait was slow and labored, with clonic tremors of the stiffly moved legs. (Figs. 9 and 10). The cerebrospinal fluid was normal. Blood count: Rbc. 4.2 million, Hb 90 per cent, C.I. 1.06.

Neurological Diagnosis: Nutritional spastic syndrome.

Case 8. Pte. F. L., aged 26 years. Captured at Singapore February 1942. He began to drag the left leg in walking in November 1942 and at the same time noticed his vision was

deteriorating. By December 1942 he had lost all useful movement in both feet and the left arm. He described his diet at this time as consisting of rice, green soup and of potato tops, with an occasional small piece of meat and palm cabbage. He gradually lost useful movement in both hands but following treatment with red palm oil and marmite (yeast extract) his vision began to improve after 3 days, his arms after 3 weeks. His lower limbs remained paralysed until treatment with liver extract parenterally on release. In the ensuing 3 weeks some recovery of motor power had occurred.

On examination in September 1945 his speech was found to be slightly dysarthric and he had a severe spastic paraplegia. There was doubtful pallor of the optic discs. The jaw jerk was increased, the tendon jerks greatly exaggerated in both upper and both lower limbs. There was slight spasticity in the flexors of the wrist and elbow, and moderately severe spasticity in both lower limbs. The abdominal reflexes were absent, the plantar responses extensor. There was no loss of sensation. Sphincter control had been maintained throughout the illness.

Neurological Diagnosis: Nutritional spastic syndrome.

Case 9. V. S., Indian Sepoy, prisoner in Malaya, developed an illness in ? 1943 for which he now has poor memory (probably Wernicke syndrome). On recovery he found he had severe loss of the use of his lower limbs and hands with extreme tenderness of the muscles and painful paresthesias. The condition had been stationary for 2 years during which the pains had subsided but no recovery of motor function had occurred. On examination in September 1945 vision was not affected and speech was normal. There was severe foot- and wrist-drop with contractures (figs. 4 and 5) with wasting of all the muscles in the limbs, but particularly those distal to elbow and knee, and loss of all tendon jerks. The only loss of sensation that could be demonstrated was a mild hypesthesia and hypalgesia below the knees. The calf muscles were extremely tender and thigh and forearm-muscles remained tender to pressure over the region of nerve termination.

Neurological Diagnosis: Severe chronic beriberi neuritis with contracture.

Case 10. A. K., Indian Sepoy, prisoner in Malaya, lost the use of the lower limbs in the course of some 2 to 3 weeks in 1943 and developed difficulty in micturition soon afterwards. He had remained bedridden since. On examination in September 1945 there was some uncertainty in vision for small objects but the optic discs showed no pallor. Speech was unaffected, but there was a bilateral facial weakness with inability to close the eyes tightly or whistle. Motor power was otherwise excellent for all movements, including dorsiflexion of the feet, and there was no wasting of muscles, or muscular tenderness. The knee jerks were both absent, ankle jerks both absent, plantar responses flexor. Vibration sense was lost below the costal margins, position sense lost in the toes. There was no loss of sphincter control. The gait was grossly ataxic and he was unable to stand unsupported (figs. 7 and 8).

Neurological Diagnosis: Nutritional spinal ataxia, with facial diplegia and doubtful retrobulbar neuritis.

Case 11. S. D., Indian Gunner, prisoner in Malaya, had developed unsteadiness in walking gradually in December 1944, following severe dysentery lasting 2 months. There had been no loss of vision or footdrop.

On examination the only abnormality found in the cranial nerves was a hoarse weak voice. There was no loss of muscular power in the limbs and no wasting of muscles or tenderness. The knee jerks were absent, the ankle jerks also. The right plantar response was flexor, the left extensor. There was slight blunting of sensation to pin prick below the knees, but complete absence of vibration sense in the lower limbs with gross impairment of position sense. There was no loss of control of sphincters. The gait was mildly ataxic

(figs. 11 and 12) with clonic tremulous movement of each limb. He was unable to stand without support.

Neurological Diagnosis: Nutritional spinal ataxia, with aphonia.

Case 12. R. U., Indian Sepoy, prisoner in Malaya, developed severe burning sensation in the soles of the feet in September 1944 followed by a sensation of numbness which spread "all over" him from the feet upwards, with some unsteadiness in walking but without loss of use of the limbs. After some months the numbness gradually receded and the burning sensation lessened. He regained steadiness in walking, but the soles of the feet still burn at night. On examination vision, speech and gait were natural. There was no loss of motor power or wasting. The knee jerks were present and brisk, the ankle jerks absent. No loss of sensation was found, and nothing objective could be discerned in the feet.

Neurological Diagnosis: "Burning feet" (Acrodynia).

Case 13. A. D., a civilian interned in South Burma from June 1942 to release in August 1945 had malaria in July 1942 with many subsequent relapses, dysentery in August 1942, and swollen legs from September 1942 to April 1943. He had recurrent ulceration of the legs from December 1942 to February 1944. In May 1943 he first noticed the gradual onset of visual defect with inability to read. Some improvement in vision occurred with milk and liver supplements to diets in July 1943 with further worsening March 1944 to August 1944 when milk was again unavailable. In August 1944 he began to scrape his toes on the ground and trip over objects. By October 1944 he began to stagger in walking, with weakness in knees and hands. Shooting pains began in the legs and feet followed by numbness of the feet. A transient improvement followed the temporary addition of milk and rats (*sic*) to his diet. Change in voice was first noted in February 1945 and some dysphagia but no nasal regurgitation. Hearing began to fail in April 1945 with slight tinnitus and bilateral deafness. There was no vertigo. On examination (September 1945) he was normal mentally. Visual acuity was 6/18 R, 6/12 L with bilateral small central scotoma and slight temporal pallor of both discs. There was slight bilateral deafness of central type. He sometimes choked in swallowing food. His voice was of hoarse blowing quality and the vocal cords showed poor adduction and abduction. The upper limbs were normal. In the lower limbs there was slight wasting of the anterior tibial muscles with bilateral footdrop and gross weakness of dorsiflexion of the ankle and toes. Movements at the knee and hip were performed well. There was no spasticity. Both knee jerks were brisk, and ankle jerks present. The plantar responses were flexor, the abdominal reflexes present and equal. There was a patchy impairment to pin prick and light touch sensation below a fading level just above the knees. Position sense in the feet was absent, vibration sense absent in the ankles and knees, diminished on the iliac crests, and normal in the hands. The calves were mildly tender. The gait was of high steppage variety with bilateral footdrop and severe ataxia in addition. There was pronounced Rombergism. Sphincter control was not affected.

Neurological Diagnosis: Nutritional retrobulbar neuritis with ataxia, deafness, aphonia and dysphagia, and in addition old beriberi polyneuritis.

BIBLIOGRAPHY

1. Abel, A. R., Backus, R. W., Bourquin, H. and Gerard, R. W.: Tryptophan and thyroid function. Amer. J. Physiol. 73: 287–295, 1925.
2. Acton, H. W.: Causation of Lathyrism in man. Indian Med. Gaz. 57: 241–247, 1922.
3. Adams, R. D. and Kubik, C. S.: Subacute degeneration of the brain in pernicious anemia. New Engl. J. Med. 231: 2–9, 1944.
4. Adolph, W. H., Greaves, A. V., Lawney, J. C. and Robinson, H. L.: Nutritional disorders in Japanese internment camps. War Medicine 5: 349–355, 1944.

5. ALBERT, J.: Studies on infantile beriberi based on five hundred fourteen cases. Philippine J. Sci. 45: 297–318, 1931.
6. ALCANTARA, V. C. AND DE OCAMPO, G.: The larynx in infantile beriberi. Arch. Otolaryngol. 30: 389–399, 1939.
7. ANDERSON, P. V. AND SPILLER, W. G.: Pellagra, with a report of two cases with necropsy. Amer. J. Med. Sci. 141: 94–106, 1911.
8. ANDERSON, L. A. P., HOWARD, A. AND SIMONSEN, J. L.: Studies in lathyrism. Indian J. Med. Res. 12: 613–643, 1925.
9. ANTOPOL, W. AND TARLOV, I. M.: Experimental study of the effects produced by large doses of vitamin B_1. J. Neuropath. Exp. Neur. 1: 330–336, 1942.
10. ANTOPOL, W. AND UNNA, K.: Pathologic aspect of nutritional deficiencies in rats. 1. Lesions produced by diets free of vitamin B_6 (Pyridoxine) and the response to vitamin B_6. Arch. Path., Chic. 33: 241–253, 1942.
11. ARING, C. D., EVANS, J. P. AND SPIES, T. D.: Some clinical neurologic aspects of vitamin B deficiencies. J. Amer. Med. Assn. 113: 2195–2199, 1939.
12. ASTIEN, L.: *Contribution à l'Étude du Lathyrisme; Intoxication Chronique par les Gesses.* Thèse de Lyon No. 163, 1883, Pitrat Aine.
13. AUSTREOESILO, A.: Skorbutische Polyneuritis und Beriberi. Arch. f. Schiffs- und Tropen-hygiene 12: 780–789, 1908.
14. AXELROD, H. E., MORGAN, A. F. AND LEPKOVSKY, S.: The fate of tryptophane in pyridoxine-deficient and normal dogs. J. Biol. Chem. 160: 155–164, 1945.
15. AYKROYD, W. R.: Beriberi and other food deficiency diseases in Newfoundland and Labrador. J. Hygiene (Camb.) 30: 359–386, 1939.
16. AYKROYD, W. R.: The vitamin B_2 content of cereals and the supposed connection between human pellagra and deficiency of the vitamin. Biochem. J. 24: 1479–1488, 1939.
17. BASU, K. P., NATH, M. C., AND MUKHERJEE, R.: Biological value of the proteins of soya bean, field pea, and lathyrus sativa; by the balance sheet and growth methods. Indian J. Med. Res. 24: 1001–1026, 1937.
18. BASU, K. P., NATH, M. C., GHARI, M. C. AND MUKHERJEE, R.: Extraction and chemical analysis of the proteins of green gram (Phaseolus Mungo), lentil (Lens Esculenta) and lathyrus sativa (Khesari). Indian J. Med. Res. 24: 1027–1042, 1937.
19. BELMONDO, E.: Le alterazioni anatomiche del midollo spinale nella pellagra. Rif. Med. 5: 1532–1534, 1889.
20. BENTLEY, A. J. M.: *Bèri-bèri: its etiology, symptoms, treatment and pathology.* Edinburgh, 1893, Y. J. Pentland.
21. BICKEL, H.: Funikuläre Myelitis mit bulbären und polyneuritischen Symptonen. Arch. Psychiat. Nervenkr. 53: 1106–1117, 1914.
22. BIETTI, A.: Ueber Augenveränderungen bei Pellagra. Klin. Monatsbl. Augenheilk. Stuttgart 31: 337–350, 450–462, 1901.
23. BIGOAM, A. G. AND GHALIOUNOUI, P.: Pellagra: its clinical features and pathology. Lancet, Lond. 2: 1198–1200, 1933.
24. BILLON, E.: *Traité de la Pellagre.* Paris, 1865. V. Masson et Fils.
25. BOAS, M. A.: The effect of desiccation upon the nutritive properties of egg-white. Biochem. J. 21: 712–724, 1927.
26. BONHURANT, E. D.: Endemic multiple neuritis. New York Med. J. 66: 685–691, 728–732, 1897.
27. BONTIUS, JAMES: *An Account of the Diseases, Natural History and Medicines of the East Indies* (Translation of Jacobus Bontius, *De Medicina Indorum* 1642) Lond. 1769 T. Noteman.
28. BOUCHARD: Etude d'anatomie pathologique sur un cas de pellagra; Lésions de la moelle épiniere, du coeur et du foie. Gaz. Méd, de Paris 19: 599–600, 1864.
29. BOWMAN, K. M. AND WORTIS, H.: Psychiatric syndromes caused by nutritional deficiency. Proc. Assn. Res. Nerv. Ment. Dis. 22: 168–191, 1943.

30. Box, C. R. and Mott, F. W.: Fatal pellagra in two English boys, with the results of pathological examination of one case. Trans. Roy. Soc. Trop. Med. Hyg. 6: 149–160, 1912.
31. Braddon, W. L. and Cooper, E. A.: The influence of the total fuel-value of a dietary upon the quantity of vitamin required to prevent beri-beri. Brit. Med. J. 1: 1348–1349, 1914.
32. Brinton, D.: An unusual form of epidemic food-poisoning with neurological symptoms. Proc. Roy. Soc. Med. Lond. 39: 173–175, 1946.
33. Brunelli, Dr.: Sur une cause peu connue de la tabes dorsale spasmodique. Trans. VIIth. International Medical Congress, London 2: 45–47, 1881.
34. Buchanan, W. J.: A note on lathyrism. J. Trop. Med. (Hyg.) 1: 261–262, 1899.
35. Bullmore, C.: Beri-beri. Lancet, Lond. 2: 873–875, 1900.
36. Burgess, R. C., Cruickshank, E. K. and Williams, C.: Nutritional experiences in prisoners of war and internment camps in the Far East. Lancet, Lond. 1: 852–853, 1946.
37. Butler, A., Ruffin, J. M., Sniffen, M. M. and Wickson, M. E.: The nutritional status of civilians rescued from Japanese prison camps. New Engl. J. Med. 233: 639–651, 1945.
38. Buzzard, E. F. and Greenfield, J. G.: *Pathology of the Nervous System.* London 1921. Constable and Coy. (p. 232)
39. Calhoun, F. P.: Alterations in the visual fields associated with pellagra. Amer. J. Ophthal. 1: 834–847, 1918.
40. Campbell, A. C. P. and Biggart, J. H.: Wernicke's encephalopathy (polioencephalitis superior): Its alcoholic and non-alcoholic incidence. J. Path. Bact. 48: 245–262, 1939.
41. Cantani, A.: Latirismo (Lathyrismus). Morgagni 15: 745–765, 1873.
42. Chamberlain, W. P., Bloombergh, H. D. and Kilbourne, F. D.: A study of the influence of rice diet and of inanition on the production of multiple neuritis of fowls and the bearing thereof on the etiology of beri-beri. Philippine J. Sci. Sect. B., 6: 177–209, 1911.
43. Chantemesse (Dr.) and Raymond (Dr.): Une épidémie de paralysis ascendante chez les aliénés. Ann. Inst. Pasteur 12: 574–590, 1898.
44. Chardon, M.: De l'acrodynie. Rev. Méd. Franç. Ètr. 3: 51–74 and 374–396, 1830.
45. Chevers, N.: Practical notes on the ordinary diseases of India, especially those prevalent in Bengal. Med. Times Gaz. 1: 75–78, 1884.
46. Chick, H.: The results of laboratory work on vitamin B deficiency in relation to clinical experience. Proc. Roy. Soc. Med. Lond. 27: 473–478, 1933–4.
47. Chick, H., El-Sadr, M. M. and Worden, A. N.: Occurrence of fits of an epileptiform nature in rats maintained for long periods on a diet deprived of vitamin B_6. Biochem. J. 34: 595–600, 1940.
48. Church, C. F.: Functional studies of the nervous system in experimental beriberi. Amer. J. Physiol. 111: 660–680, 1935.
49. Clark, A.: On the aetiology of pellagra and allied nutritional diseases. West African Med. J. 8 (No. 4) 7–9, 1935 (November).
50. Clark, A.: Concerning Riboflavin. J. Trop. Med. (Hyg.) 44: 15–17, 1941.
51. Clark, A.: Concerning Nicotinie Acid: On nutritional effects of inhibitory factorsin food. J. Trop. Med. (Hyg.) 44: 126–129, 1941.
52. Clarke, C. A. and Sneddon, I. B.: Nutritional neuropathy in prisoners-of-war and internees in Hong-Kong. Lancet, Lond. 1: 734–737, 1946.
53. Cleckley, H. M., Sydenstricker, V. P. and Geeslin, L. E.: Nicotinic acid in the treatment of atypical psychotic states associated with malnutrition. J. Amer. Med. Assn. 112: 2107–2110, 1939.

54. Cohen, H.: Optic atrophy as the presenting sign in pernicious anemia. Lancet, Lond. 2: 1202–1203, 1936, and
Courville, C. B. and Nielsen, J. M.: Optic atrophy associated with subacute combined degeneration of the spinal cord. Bull. Los Angeles Neurol. Soc. 3: 83–88, 1938.
55. Compton, K. T.: Some contributions from the sister sciences. J. Amer. Med. Assn. 131: 77–80, 1946.
56. Covell, W. P.: Pathologic changes in the peripheral auditory mechanism due to avitaminoses (A, B complex, C, D and E). Laryngoscope, St. Louis, 50: 632–647, 1940.
57. Cowgill, G. R.: *The Vitamin B Requirement of Man.* New Haven, 1935, Yale Univ. Press.
58. Craig, W. McK. and Horton, B. T.: Diagnosis and treatment of vascular disorders of the extremities. Surg. Clin. N. Amer. 18: 899–934, 1938.
59. Dandenfield, H. V.: *Le Béribéri.* Paris 1905. A. Maloine.
60. Davin, C. Contribution à l'étude du vertige paralysant. Rev. Méd. Suisse Rom. 7: 65–72, 1887.
61. Davison, C.: Disseminated demyelination of the central nervous system in monkeys and allied disorders in man. J. Neurol. Psychopath. 14: 227–238, 1934.
62. Davison, C. and Stone, L.: Lesions of the nervous system of the rat in vitamin B deficiency. Arch. Path., Chic. 23: 207–223, 1937.
63. Dawson, J. B.: Nystagmus associated with hyperemesis gravidarum. J. Obstet. Gynaec., Brit. Emp. 44: 731–732, 1937.
64. Dieren, E. Van.: *Meel-Vergiftigingen.* Amsterdam 1997 Scheltema und Holkema.
65. Dillino, W. J.: The constituents of Lathyrus sativus and their action. J. Pharmacol. 14: 359–366, 1920.
66. Duodale, J. N.: "Burning feet" and other problems in estate medical practice. Malayan Med. J. 3: 74–76, 1928.
67. Dürck, H.: Untersuchungen über die pathologische Anatomie der Beri-beri. Ein Beitrag zur normalen und pathologischen Anatomie des peripherischen Nervensystems. Suppl. 8 Bd., Aschoff'e Beitr. path. Anat. Jena 1908.
68. Dychitan, T.: Contribution to the work on lapnus from the point of view of its epidemiology and history of its discovery. J. Philippine Isl. Med. Assn. 10: 481–487, 1930.
69. Earle, K. V.: Polyneuritis in Trinidad Oil workers. J. Trop. Med. (Hyg.) 44: 150–152, 1941.
70. Ekbom, K-A.: *Restless legs.* Acta Medica Scand. Suppl. 158: Stockholm 1945.
71. Ellinger, P., Hassan, A. ann Taha, M. M.: Pellagra in Egypt. Lancet, Lond. 2: 755–758, 1937.
72. Elliott, R. H.: *Tropical Ophthalmology.* London 1920, Henry Frowde.
73. Elvehjem, C. A.: Relationship of enzymes to deficiency. Proc. Ass. Res. Nerv. Ment. Dis. 21: 13–28, 1943.
74. Engel, R. W. ann Phillips, P. H.: The lack of nerve degeneration in uncomplicated vitamin B_1 deficiency in the chick and the rat. J. Nutrit. 16: 585–596, 1938.
75. Féris, Dr.: Le béribéri d'après les travaux brésiliens. Arch. Méd. Nav. 37: 466–478, 1882 and 38: 50–69, 1882.
76. Filiminoff, I. N.: Zur pathologisch-anatomischen Charakteristik des Lathyrismus. Zschr. ges. Neurol. Psychiat. 105: 76–92, 1926.
77. Fraser, H. ann Stanton, A. T.: The etiology of beriberi. Philippine J. Sci. 5 B: 55–61, 1910.
78. Fraser, H. ann Stanton, A. T.: *Collected Papers on Beri-beri.* Studies from the Institute for Medical Research, Federated Malay States No. 17, London 1924, John Bale.

79. Fumarola, G. and Zanelli, C. F.: Anatomische-experimentelle Forschungen über den Lathyrismus. Arch. Psychiat. Nervenkr. 54: 489–536, 1914.
80. Garland, H. G.: A central nervous deficiency syndrome. Proc. Roy. Soc. Med., Lond. 39: 178–180, 1946.
81. Gaucher, Dr. and Sergent, E.: Note sur les lésions histologiques viscérales de la pellagre. Bull. Soc. méd. Hôp. Paris. 12: 552–558, 1895.
82. Geiger, B. J., Steenbock, H. and Parsons, H. T.: Lathyrism in the rat. J. Nutrit. 6: 427–442, 1933.
83. Gerlier, (Dr.): Une épidémie de vertige paralysant. Rev. méd. Suisse Rom. 7: 5–29, 1887.
84. Gerrard, P. N.: *Beri-beri: Its Symptoms and Symptomatic Treatment.* London 1904, J. and A. Churchill.
85. Goldberger, J. and Tanner, W. F.: Amino-acid deficiency probably the primary etiological factor in pellagra. Pub. Health Rep., Wash. 37: 462–486, 1922.
86. Goldberger, J. and Tanner, W. F.: A study of the treatment and prevention of pellagra. Pub. Health Rep., Wash. 39: 87–107, 1924.
87. Goldberger, J. and Tanner, W. F.: A study of the pellagra-preventive action of dried beans, casein, dried milk and brewers yeast, with a consideration of the essential preventive factors involved. Pub. Health Rep., Wash., 40: 54–83, 1925.
88. Goldberger, J. and Wheeler, G. A.: Experimental pellagra in white male convicts. Arch. Intern. Med. 25: 451–471, 1920.
89. Grande Covian, F. and Jiminez Garcia, F.: Lactacidemia y pruebas de sobrecarga de lactato, en los pacientes carencides de Madrid. Rev. Clin. espãn. 5: 29–32, 1942.
90. Grandjean, M.: Paralysie ataxique observée chez des Kabyles, a la suite de l'ingestion d'une variété de gesse. Arch. Méd. Pharm. mil. 1: 95–102, 1895.
91. Green, R. G., Carlson, W. E. and Evans, C. A.: The inactivation of vitamin B_1 in diets containing whole fish. J. Nutrit. 23: 165–174, 1942.
92. Greenfield, J. G. and Carmichael, E. A.: The peripheral nerves in cases of subacute combined degeneration of the cord. Brain 58: 483–491, 1935.
93. Greenfield, J. G. and Holmes, J. M.: Case of pellagra; pathological changes in spinal cord. Brit. med. J. 1: 815–819, 1939.
94. Grierson, J.: On the burning of the feet of natives. Trans. Med.-Physical Soc., Calcutta 2: 275–281, 1826
95. Guillain, G., Bertrand, I., Mollaret, P., and Lereboullet, J.: Étude anatomique d'un cas français de pellagre avec paraplègie. Bull. Soc. Méd. Hôp, Paris 50: 650–657, 1934.
96. György, P.: Vitamin B_2 and the pellagra-like dermatitis in rats. Nature, Lond. 133: 498–499, 1934.
97. György, P., Rose, C. S., Eakin, R. E., Snell, E. E. and Williams, R. J.: Egg-white injury as the result of nonabsorption or inactivation of biotin. Science 93: 477–478, 1941.
98. Hamelin, E.: *Gesse.* Article in *Dict. Encyclop. des Sciences Médicales* 44: 642–649, 1882.
99. Handler, P.: Use of highly purified rations in the study of nicotinic acid deficiency. Proc. Soc. Exp. Biol. Med. 52: 263–264, 1943.
100. Harris, H. F.: *Pellagra.* New York 1919, Macmillan Company.
101. Holst, A.: Experimental studies relating to "ship-beri-beri" and scurvy. J. Hyg., Camb. 7: 619–633, 1907.
102. Hou, H. C. and Yu, C. M.: Beriberi in ancient Chinese medical literature. Chinese Med. J. 58: 302–313, 1940.
103. Huber, J. Ch.: Historische Notiz über den Lathyrismus. Friedreich's Blätt. gerichtl. Med. Sanitätsp. 37: 34–36, 1886.
104. Huches, W.: Food yeast in tropical nutrition. Lancet, Lond. 1: 569–572, 1946.

105. Husemann, Th.: Ueber einige Producte des gefaulten Mais. Arch. exp. Path. Pharm. 9: 226–288, 1878.
106. Ironside, R.: Neuritis complicating pregnancy. Proc. Roy. Soc. Med., Lond., 32: 588–595, 1939.
107. Irvine, J.: Notice of a form of paralysis of the lower extremities extensively prevailing in part of the district of Allahabad, produced by the use of Lathyrus sativus as an article of food. Indian Ann. Med. Sci., 6: 424–434, 1859.
108. Irvine, J.: Further notices of paraplegia caused by the use of Kassaree dal (Lathyrus sativus) in the Mirzapore district and in other parts of India. Indian Ann. Med. Sci. 7: 501–502, 1861.
109. Irvine, J.: Notice of paraplegia caused by the use of Lathyrus sativus in the various districts of the north-western provinces of India. Indian Ann. Med. Sci. 12: 89–124, 1868.
110. Itoh, M.: Ueber Pellagra in Japan. Trans. 6th Biennial Congress, Far Eastern Assoc. Trop. Med., Tokyo, 1: 315–333, 1925.
111. Jeanselme, E.: *Le Béribéri*. Paris, 1906, Masson et Cie.
112. Jiménez Díaz, C., Ortiz de Landazuri, E. and Rona, E.: Estudios sobre el latirismo: Síntesis de datos clinicos y experimentales para el conocimiento de la patogenia del latirismo. Rev. clin. espân. 8: 154–166, 1943.
113. Jolliffe, N., Bowman, K. M., Rosenblum, L. A. and Fein, H. D.: Nicotinic acid deficiency encephalopathy. J. Amer. Med. Assn. 114: 307–312, 1940.
114. Jolliffe, N., Goodhart, R., Gennis, J. and Clive, J. K.: The experimental production of vitamin B_1 deficiency in normal subjects. Amer. J. Med. Sci. 198: 198–211, 1930.
115. Kagawa, S.: Studies on the relation of neuritis axialis to beriberi in Japan. Japanese J. Med. Sciences (sect. VIII) 5: 1–16, 17–41, 43–60, 1938.
116. Kanasugi, H.: Die Kehlkopfstorungen bei Beriberi. Berl. Klin. Wschr. 45: 1034–1086, 1908.
117. Katz, C. J.: Neuropathologic manifestations found in a Japanese prison camp. J. Nerv. Ment. Dis. 103: 456–465, 1946.
118. Kernohan, J. W. and Kennedy, R. L. J.: Acrodynia (So-called). Amer. J. Dis. Child. 36: 341–351, 1928.
119. Keys, A., Taylor, H. L., Mickelsen, O. and Henschel, A.: Famine edema and the mechanism of its formation. Science 103: 669–670, 1946.
120. Kohn, H. I., Klein, J. R. and Dann, W. J.: The V-factor content and oxygen consumption of tissues of the normal and blacktongue dog. Biochem. J. 33: 1432–1442, 1939.
121. Kozowsky, A. D.: Die Pellagra: Pathologisch-anatomische Untersuchung. Arch. Psychiat. Nervenkr. 49: 204–241, 556–614, and 873–935, 1912
122. Krehl, W. A., Sarma, P. S. and Elvehjem, C. A.: The effect of protein on the nicotinic acid and tryptophane requirement of the growing rat. J. Biol. Chem. 162: 403–411, 1946.
123. Krehl, W. A., Tepley, E. J. and Elvehjem, C. A.: Effect of corn grits on nicotinic acid requirements of the dog. Proc. Soc. Exp. Biol. and Med. 58: 334–337, 1945.
124. Krehl, W. A., Tepley, L. J., Sarma, P. S. and Elvehjem, C. A.: Growth-retarding effect of corn in nicotinic acid-low rations and its counteraction by tryptophane. Science 101: 489–490, 1945.
125. Lancet Editorial: The fresh loaf. Lancet, Lond. 1: 694, 1946.
126. Landor, J. V. and Pallister, R. A.: Avitaminosis B_2. Trans. Roy. Soc. Trop. Med. Hyg. 29: 121–134, 1935.
127. Lanoenbeck, K.: Neuritis retrobulbaris und Allgemeinerkrankungen. v. Graefe's Arch. Ophth. 87: 226–279, 1914.
128. Lanoworthy, O. R.: Lesions of the nervous system characteristic of pellagra. Brain 54: 291–302, 1931.

79. Fumarola, G. and Zanelli, C. F.: Anatomische-experimentelle Forschungen über den Lathyrismus. Arch. Psychiat. Nervenkr. 54: 489–536, 1914.
80. Garland, H. G.: A central nervous deficiency syndrome. Proc. Roy. Soc. Med., Lond. 39: 178–180, 1946.
81. Gaucher, Dr. and Sergent, E.: Note sur les lésions histologiques viscérales de la pellagre. Bull. Soc. méd. Hôp. Paris. 12: 552–558, 1895.
82. Geiger, B. J., Steenbock, H. and Parsons, H. T.: Lathyrism in the rat. J. Nutrit. 6: 427–442, 1933.
83. Gerlier, (Dr.): Une épidémie de vertige paralysant. Rev. méd. Suisse Rom. 7: 5–29, 1887.
84. Gerrard, P. N.: *Beri-beri: Its Symptoms and Symptomatic Treatment.* London 1904, J. and A. Churchill.
85. Goldberger, J. and Tanner, W. F.: Amino-acid deficiency probably the primary etiological factor in pellagra. Pub. Health Rep., Wash. 37: 462–486, 1922.
86. Goldberger, J. and Tanner, W. F.: A study of the treatment and prevention of pellagra. Pub. Health Rep., Wash. 39: 87–107, 1924.
87. Goldberger, J. and Tanner, W. F.: A study of the pellagra-preventive action of dried beans, casein, dried milk and brewers yeast, with a consideration of the essential preventive factors involved. Pub. Health Rep., Wash., 40: 54–83, 1925.
88. Goldberger, J. and Wheeler, G. A.: Experimental pellagra in white male convicts. Arch. Intern. Med. 25: 451–471, 1920.
89. Grande Covian, F. and Jiminez Garcia, F.: Lactacidemia y pruebas de sobrecarga de lactato, en los pacientes carencides de Madrid. Rev. Clín. espãn. 5: 29–32, 1942.
90. Grandjean, M.: Paralysie ataxique observée chez des Kabyles, a la suite de l'ingestion d'une variété de gesse. Arch. Méd. Pharm. mil. 1: 95–102, 1895.
91. Green, R. G., Carlson, W. E. and Evans, C. A.: The inactivation of vitamin B_1 in diets containing whole fish. J. Nutrit. 23: 165–174, 1942.
92. Greenfield, J. G. and Carmichael, E. A.: The peripheral nerves in cases of subacute combined degeneration of the cord. Brain 58: 483–491, 1935.
93. Greenfield, J. G. and Holmes, J. M.: Case of pellagra; pathological changes in spinal cord. Brit. med. J. 1: 815–819, 1939.
94. Grierson, J.: On the burning of the feet of natives. Trans. Med.-Physical Soc., Calcutta 2: 275–281, 1826
95. Guillain, G., Bertrand, I., Mollaret, P., and Lereboullet, J.: Étude anatomique d'un cas français de pellagre avec paraplègie. Bull. Soc. Méd. Hôp, Paris 50: 650–657, 1934.
96. György, P.: Vitamin B_2 and the pellagra-like dermatitis in rats. Nature, Lond. 133: 498–499, 1934.
97. György, P., Rose, C. S., Eakin, R. E., Snell, E. E. and Williams, R. J.: Egg-white injury as the result of nonabsorption or inactivation of biotin. Science 93: 477–478, 1941.
98. Hamelin, E.: *Gesse.* Article in *Dict. Encyclop. des Sciences Médicales* 44: 642–649, 1882.
99. Handler, P.: Use of highly purified rations in the study of nicotinic acid deficiency. Proc. Soc. Exp. Biol. Med. 52: 263–264, 1943.
100. Harris, H. F.: *Pellagra.* New York 1919, Macmillan Company.
101. Holst, A.: Experimental studies relating to "ship-beri-beri" and scurvy. J. Hyg., Camb. 7: 619–633, 1907.
102. Hou, H. C. and Yu, C. M.: Beriberi in ancient Chinese medical literature. Chinese Med. J. 58: 302–313, 1940.
103. Huber, J. Ch.: Historische Notiz über den Lathyrismus. Friedreich's Blätt. gerichtl. Med. Sanitätsp. 37: 34–36, 1886.
104. Huches, W.: Food yeast in tropical nutrition. Lancet, Lond. 1: 569–572, 1946.

157. Moore, D. G. F.: Retrobulbar neuritis cum avitaminosis. West African Med. J. 7: 119–120, 1934.
158. Moore, D. F.: Nutritional retrobulbar neuritis followed by partial optic atrophy. Lancet, Lond. 1: 1225–1227, 1937.
159. Moore, D. G. F.: Retrobulbar neuritis cum avitaminosis. West African Med. J. 9: (No. 2): 35–40, 1937.
160. Moore, D. F.: Pellagra or pellagra-like conditions in association with deficiency in vitamin A. J. Trop. Med. (Hyg.) 43: 190–194, 1940.
161. Moore, D. F.: Allowable claims for vitamin A deficiency: The relation of visual defects and skin lesions. J. Trop. Med. (Hyg.) 44: 47–48, 1941.
162. Morgan, M. T.: Report on an outbreak of alleged ergot poisoning by rye bread in Manchester. J. Hyg., Camb. 29: 51–61, 1929–30.
163. Mossé, A. and Destarac, J.: Contribution à l'étude du héribéri. Rev. Médicine 15: 977–1008, 1895.
164. Musselman, M. M.: Nutritional diseases in Cabanatuan. War Medicine 8: 325–332, 1945.
165. Naoayo, M. and Fujii, S.: Reisfütterungsversuch bei Affen zwecks Erzeugung der Beriberi ähnlichen Erkrankung. Verhand. Japan. Patholog. Gesellsch. Tokyo, 39–43, 1912.
166. Ness, H. T., Price, E. L. and Parsons, H. T.: Thiamine depletion of human subjects on a diet rich in thiamine. Science 103: 198–199, 1946.
167. Neusser, B.: *Die Pellagra in Oesterreich und Rumanien.* Wien, 1887. (Quoted by Tuczek).
168. Nicholls, L.: Phrynoderma: A condition due to vitamin deficiency. Indian Med. Gaz. 68: 681–687, 1933.
169. Nicholls, L.: A study of vitamin A deficiency in Ceylon with special reference to the statistical incidence of phrynoderma and sore mouth. Indian Med. Gaz. 69: 241–251, 1934.
170. Nicholls, L.: Nerve and cord degeneration referable to vitamin A deficiency. Indian Med. Gaz. 70: 550–552, 1935.
171. Nocht, B.: Ueber Segelschiff-Beriberi in *Festschrift zum sechzigsten Geburtstage von Robert Koch.* p. 203–218. Jena, 1903, G. Fischer.
172. Norman, C.: On beri-beri occurring in temperate climates. Brit. Med. J. 2: 872–876, 1898 and 2: 686, 1899.
173. Pallister, R. A.: Ataxic paraplegia occurring amongst Chinese in Malaya. Trans. Roy. Soc. Trop. Med. Hyg. 34: 203–211, 1940.
174. Pappenheimer, A. M.: Effects of vitamin E deprivation in various laboratory animals. Proc. Assn. Res. Nerv. Ment. Dis. 21: 85–100, 1943.
175. Paterson, D. and Greenfield, J. G.: Erythroedema polyneuritis. Quart. J. Med. 17: 6–18, 1923–4.
176. Pauly, R. and Deprecq, M.: Pellagra et troubles nerveux. J. Méd. de Bordeaux 116: 145–156 and 185–194, 1939.
177. Pekelharing, C. A. and Winkler, C.: *Beri-beri: Researches concerning its Nature and Cause, and the Means of its Arrest.* English trans. by J. Cantlie. London 1893, John Bale Sons and Danielsson.
178. Pentshew, A.: Ueber die Histopathologie des Zentralnervensystems bei der Psychosis Pellagra. Zschr. ges. Neurol. Psychiat. 118: 17–48, 1929.
179. Phillips, P. H. and Engel, R. W.: Some histopathologic observations on chicks deficient in the chick antidermatitis factor or pantothenic acid. J. Nutrit. 18: 227–232, 1939.
180. Platt, B. S. and Gin, S. Y.: Some observations on a preliminary study of beriberi in Shanghai. Trans. IX Cong. Far East Assn. Trop. Med. 2: 407–413, 1934.
181. Prados, M. and Swank, R. L.: Vascular and interstitial cell changes in thiamine-deficient animals. Arch. Neurol. Psychiat., Chic. 47: 626–644, 1942.

129. LIPPINCOTT, S. W. AND MORRIS, H. P.: Morphologic changes associated with pantothenic acid deficiency in the mouse. J. Nat. Cancer Inst. 2: 39–46, 1941.
130. LITTLE, J. M.: Beriberi. J. Amer. Med. Assn. 63: 1287–1290, 1914.
131. LOMBROSO, C.: *Trattato Profilattico e Clinico della Pellagra.* Torino, 1892, Fr. Bocca.
132. LOVELACE, C.: The etiology of beriberi. J. Amer. Med. Assn. 59: 2134–2137, 1912.
133. LUKÁS, H. AND FABINYI, R.: Zur pathologischen Anatomie der Pellagra. Allg. Zeitschr. Psychiat., Berl. 65: 657–665, 1908.
134. MCCARRISON, R.: A note on lathyrism in the Gilgit Agency. Indian J. Med. Res. 14: 379–381, 1926.
135. MCCARRISON, R. AND KRISHNAN, B. G.: Lathyrism in the rat. Indian J. Med. Res. 22: 65–66, 1934.
136. MCCOLLUM, E. V., ORENT-KEILES, E. AND DAY, H. G.: *The Newer Knowledge of Nutrition.* Fifth Edition, New York, 1939. The Macmillan Company.
137. MCCOWAN, P. K.: Pellagra: A report of four cases with histological findings in one case. J. Mental Sci. 70: 410–422, 1924.
138. MALCOLMSON, J. G.: *A Practical Essay on the History and Treatment of Beriberi.* Madras, 1835, Vepery Mission Press.
139. MALCOLMSON, J. G.: *Observations on Some Forms of Rheumatism Prevailing in India.* Madras, 1835, Vepery Mission Press.
140. MARIE, PIERRE: Lathyrism et béribéri. Progrés Méd., Paris. 11: 842–845, 1883.
141. MARINESCO, G.: Lésions des centres nerveux dans la pellagra. Compt. rend. Soc. Biol., Paris. Sér. 11, 1: 919–921, 1899.
142. MARSHALL, H.: *Notes on the Medical Topography of the Interior of Ceylon and on the Health of the Troops Employed in the Kandyan Provinces.* London, 1821, Burgess and Hill.
143. MARTIN, C.: Cobalt and other trace elements in relation to disease in Australasia (annotation: abstract). Lancet, Lond. 2: 544, 1942.
144. MATTHEWS, R. S.: Pellagra and nicotinic acid. J. Amer. Med. Assn. 111: 1148–1153, 1938.
145. MEIKLEJOHN, A. P.: Is thiamin the antineuritic vitamin? New Engl. J. Med. 223: 265–273, 1940.
146. MELLANBY, E.: The experimental production and prevention of degeneration of the spinal cord. Brain 54: 247–290, 1931.
147. MELLANBY, E.: The experimental production of deafness in young animals by diet. J. Physiol. 94: 380–398, 1938.
148. MELLANBY, E.: Skeletal changes affecting the nervous system produced in young dogs by diets deficient in vitamin A. J. Physiol. 99: 467–486, 1941.
149. MELNICK, D., HOCHBERG, M. AND OSER, B. L.: Physiological availability of the vitamins: II. The effect of dietary thiaminase in fish products. J. Nutrit. 30: 81–88, 1945.
150. METIVIER, V. M.: Eye disease due to vitamin deficiency in Trinidad. Am. J. Ophthal. 24: 1265–1280, 1941.
151. MINCHIN, R. L. H.: Primary lateral sclerosis of south India: Lathyrism without lathyrus. Brit. Med. J. 1: 253–255, 1940.
152. MINGAZZINI, G. AND BUGLIONI, G. B.: Studio clinico col anatomico sul latirismo. Rev. Sperim. Freniat. Med. Leg. 22: 79–105, 1896.
153. MIRTO, D.: Sulle alterazioni degli elementi nervosi nel latirismo spermientale acuto. Il Pisani 18: 109–128, 1897.
154. MIURA, K.: Ueber Kubisagari, ein in den nördlichen Provinzen Japans endemische Krankheit (Gerlier'sche Krankheit, vertige paralysant, vertige ptosique). Mitteil. med. Fak. Kais. Univ. Tokyo 3: 259–319, 1896.
155. MIURA, K.: Ein Fall von Recurrenslähmung bei Beri-beri mit anatomischen Befund. Dtsch. med. Wschr. 2: 1311–1312, 1909.
156. MIURA, K.: *Beri-beri.* Suppl. Bd. Nothnagel's *Spez. Pathologie und Therapie*, Wien., 1913, A. Hölder.

157. Moore, D. G. F.: Retrobulbar neuritis cum avitaminosis. West African Med. J. 7: 119–120, 1934.
158. Moore, D. F.: Nutritional retrobulbar neuritis followed by partial optic atrophy. Lancet, Lond. 1: 1225–1227, 1937.
159. Moore, D. G. F.: Retrobulbar neuritis cum avitaminosis. West African Med. J. 9: (No. 2): 35–40, 1937.
160. Moore, D. F.: Pellagra or pellagra-like conditions in association with deficiency in vitamin A. J. Trop. Med. (Hyg.) 43: 190–191, 1940.
161. Moore, D. F.: Allowable claims for vitamin A deficiency: The relation of visual defects and skin lesions. J. Trop. Med. (Hyg.) 44: 17–18, 1941.
162. Morgan, M. T.: Report on an outbreak of alleged ergot poisoning by rye bread in Manchester. J. Hyg., Camb. 29: 51–61, 1929–30.
163. Mossé, A. and Destarac, J.: Contribution à l'étude du béribéri. Rev. Médicine 15: 977–1008, 1895.
164. Musselman, M. M.: Nutritional diseases in Cabanatuan. War Medicine 8: 325–332, 1945.
165. Nagayo, M. and Fujii, S.: Reisfütterungsversuch bei Affen zwecks Erzeugung der Beriberi ähnlichen Erkrankung. Verhand. Japan. Patholog. Gesellsch. Tokyo, 39–43, 1912.
166. Ness, H. T., Price, E. L. and Parsons, H. T.: Thiamine depletion of human subjects on a diet rich in thiamine. Science 103: 198–199, 1946.
167. Neusser, B.: *Die Pellagra in Oesterreich und Rumanien.* Wien, 1887. (Quoted by Tuczek).
168. Nicholls, L.: Phrynoderma: A condition due to vitamin deficiency. Indian Med. Gaz. 68: 681–687, 1933.
169. Nicholls, L.: A study of vitamin A deficiency in Ceylon with special reference to the statistical incidence of phrynoderma and sore mouth. Indian Med. Gaz. 69: 241–251, 1934.
170. Nicholls, L.: Nervo and cord degeneration referable to vitamin A deficiency. Indian Med. Gaz. 70: 550–552, 1935.
171. Nocht, B.: Ueber Segelschiff-Beriberi in *Festschrift zum sechzigsten Geburtstage von Robert Koch.* p. 203–218. Jena, 1903, G. Fischer.
172. Norman, C.: On beri-beri occurring in temperate climates. Brit. Med. J. 2: 872–876, 1898 and 2: 680, 1899.
173. Pallister, R. A.: Ataxic paraplegia occurring amongst Chinese in Malaya. Trans. Roy. Soc. Trop. Med. Hyg. 34: 203–211, 1940.
174. Pappenheimer, A. M.: Effects of vitamin E deprivation in various laboratory animals. Proc. Assn. Res. Nerv. Ment. Dis. 21: 85–100, 1943.
175. Paterson, D. and Greenfield, J. G.: Erythrocdema polyneuritis. Quart. J. Med. 17: 6–18, 1923–4.
176. Pauly, R. and Deprecq, M.: Pellagra et troubles nerveux. J. Méd. de Bordeaux 116: 145–156 and 185–194, 1939.
177. Pekelharing, C. A. and Winkler, C.: *Beri-beri: Researches concerning its Nature and Cause, and the Means of its Arrest.* English trans. by J. Cantlie. London 1893, John Bale Sons and Danielsson.
178. Pentshew, A.: Ueber die Histopathologie des Zentralnervensystems bei der Psychosis Pellagra. Zschr. ges. Neurol. Psychiat. 118: 17–48, 1929.
179. Phillips, P. H. and Engel, R. W.: Some histopathologic observations on chicks deficient in the chick antidermatitis factor or pantothenic acid. J. Nutrit. 18: 227–232, 1939.
180. Platt, B. S. and Gin, S. Y.: Some observations on a preliminary study of beriberi in Shanghai. Trans. IX Cong. Far East Assn. Trop. Med. 2: 407–413, 1934.
181. Prados, M. and Swank, R. L.: Vascular and interstitial cell changes in thiamine-deficient animals. Arch. Neurol. Psychiat., Chic. 47: 626–644, 1942.

182. Proust, M. A.: Du lathyrisme médullaire spasmodique. Bull. Acad. Méd. Paris. **12**: 829–859, 1883 and discussion by Bouley and others pp. 866–875, 882–912, 916.
183. Putnam, J. J.: A form of poly-neuritis probably analagous to, or identical with, beri-beri, occurring in seafaring men in northern lattitudes. J. Nervous Ment. Dis. **15**: 495–505, 1890.
184. Rasch, Ch.: Ueber das Klima und die Krankheiten im Königreich Siam. Virchow's Arch. path. Anat. **140**: 327–384, 1895.
185. Ridley, J.: Account of an endemic disease of Ceylon entitled beri berri. Dublin Hosp. Rep. **2**: 227–253, 1818.
186. Righetti, R.: Polinevrite radicolare in un caso di psicosi pellagrosa. Riv. Patol. nerv. mentale **4**: 433–456, 1909.
187. Roberts, S. R.: *Pellagra.* St. Louis, 1912, C. V. Mosby Co.
188. Rodenwalt, Dr.: Pathologische Anatomie des Nervensystems bei Beriberi. Arch. Schiffs-Tropen-Hyg. **12**: (Beiheft), 31–36, 1908.
189. Sandwith, F. M.: Three fatal cases of pellagra, with examination of the spinal cords. J. Path. Bact. **7**: 460–464, 1901.
190. Scherer, H. J.: Sur une forme a evolution phasique de la leucoencéphalose périvasculaire confluente chez le macacus rhesus. Rev. Neurol. **68**: 807–822, 1937 and Zschr. ges. Neurol. Psychiat. **141**: 212–234, 1932.
191. Scheube, B.: *Die Beriberi-Krankheit.* Jena, 1894, G. Fischer.
192. Scheube, B.: *The Diseases of Warm Countries.* Trans. by Falcke, 2nd-ed. Philadelphia, 1903, Blakiston Son & Co.
193. Schob, F.: Disseminiente, Konfluierende Sklerose des Hemisphärenmarklagers des Affen Kombiniert mit Systematischer Erkrankung des Sehnerven sowie der Hinterwurzeln und Hinterstränge. Zschr. ges. Neurol. Psychiat. **135**: 95–130, 1931.
194. Schöppe, H.: Ein Fall von Neuritis retrobulbaris während der Laktation. Zschr. Augenheilk. **42**: 316–323, 1919.
195. Schuchardt, B.: Zur Geschichte und Casuistik des Lathyrismus. Dtsch. Arch. Klin. Med. **40**: 312–341, 1887.
196. Scott, H. H.: An investigation into an acute outbreak of "central neuritis." Ann. Trop. Med. Parasitol. **12**: 109–196, 1918.
197. Sebrell, W. H. and Butler, R. E.: Riboflavin deficiency in man. Pub. Health Rep., Wash. **53**: 2282–2284, 1938.
198. Sebrell, W. H. and Onstott, R. H.: Riboflavin deficiency in dogs. Pub. Health Rep., Wash. **53**: 83–94, 1938.
199. Seiffer, W.: Ein Fall von Beri-beri. Münch. med. Wschr. **47**: (1), 762–763, 1900.
200. Shah, S. R. A.: A note on some cases of lathyrism in a Punjab village. Indian Med. Gaz. **74**: 385–388, 1939.
201. Shapland, C. D.: Nutritional retrobulbar neuritis. Proc. Roy. Soc. Med. **39**: 246–249, 1946.
202. Sharples, L. R.: The condition of "burning feet" or "foot burning" in labourers on sugar plantations in the Corentyne district of British Guiana. J. Trop. Med. (Hyg.) **32**: 358–360, 1929.
203. Shaw, J. H. and Phillips, P. H.: Neuropathologic studies of pantothenic acid, biotin and folic acid complex deficiencies in the chick. J. Nutrit. **29**: 107–112, 1945.
204. Shaw, J. H. and Phillips, P. H.: Neuropathologic studies of acute and chronic thiamine deficiencies and of inanition. J. Nutrit. **29**: 113–123, 1945.
205. Shimazono, J.: Beriberi, in Stepp-György's *Avitaminosen und verwandte Krankheitszustände.* Berlin, 1927, J. Springer.
206. Shimazono, J.: Ueber die Veränderungen des Ruckenmarks und der Medulla oblongata bei Beriberi. Mitteil. med. Fak. Kais. Univ. Tokyo. **9**: 207–257, 1910.
207. Shourie, K. L.: An outbreak of lathyrism in central India. Indian J. Med. Res. **33**: 239–247, 1945.

208. Silva Lima, J. P. de: Beriberi and Sprue in Brazil. Bahia, 1872, J. B. Martin.
209. Sinclair, H. M.: Malnutrition and peripheral neuropathies. Proc. Roy. Soc. Med., Lond. 38: 172–174, 1942.
210. Singer, D. and Pollock, L. J.: Neuropathology of pellagra. Trans. Nat. Assn. Study of Pellagra. Second Meeting. p. 239–254. Columbia, S. C., 1914. R. L. Bryan Co.
211. Spies, T. D.: Pellagra: An experimental study of the skin lesions. Proc. Soc. Exp. Biol. Med. 30: 1227–1228, 1932–33.
212. Spies, R. D. and Aring, C. D.: The effect of vitamin B₁ on the peripheral neuritis of pellagra. J. Amer. Med. Assn. 110: 1081–1084, 1938.
213. Spies, T. D., Bean, W. B. and Stone, R. E.: The treatment of subclinical and classic pellagra. J. Amer. Med. Assn. 111: 584–590, 1938.
214. Spillane, J. D.: Nutritional disorders of the nervous system in the Middle East. Proc. Roy. Soc. Med., Lond. 39: 175–178, 1946.
215. Spillane, J. D.: Partial starvation in prisoners-of-war. Lancet, Lond. 2: 317–318, 1945.
216. Spillane, J. D. and Scott, G. I.: Obscure neuropathy in the Middle East. Report on 112 cases in prisoners-of-war. Lancet, Lond. 2: 261–264 (Sept.) 1945.
217. Spitzer, E. H., Coombs, A. I., Elvehjem, C. A. and Wisnicky, W.: Inactivation of thiamin by an enzyme destroyed by heat. Proc. Exp. Biol. and Med. 48: 370–379, 1941.
218. Stander, H. J.: Hemorrhagic retinitis in the vomiting of pregnancy. Surg. Gynec., Obstet. 54: 129–132, 1932.
219. Stannus, H. S.: Pellagra in Nyasaland. Trans. Roy. Soc. Trop. Med. 5: 112–119, 1911–12.
220. Stannus, H. S.: Pellagra and pellagra-like conditions in warm climates. Trop. Dis. Bull. 33: 729–741, 815–825, 885–901, 1936.
221. Stannus, H. S.: Some problems in riboflavin and allied deficiencies. Brit. Med. J. 2: 103–105 and 140–144, 1944.
222. Stockman, R.: Lathyrism. Edinburgh Med. J. 19: 277–296, and 297–307, 1917.
223. Stockman, R.: Lathyrism. J. Pharmacol. 37: 13–53, 1929.
224. Stott, H.: On the distribution of lathyrism in the United Provinces and on its cause. Indian J. Med. Res. 18: 51–55, 1930.
225. Strachan, H.: Malarial multiple peripheral neuritis. Sajou's Annual of the Universal Medical Sciences 1: 139–141, 1888.
226. Strachan, H.: On a form of multiple neuritis prevalent in the West Indies. Practitioner 59: 477–484, 1897.
227. Strauss, M. B.: Multiple neuritis. Differentiation of nutritional polyneuritis from other multiple neuritis. Proc. Ass. Res. Nerv. Ment. Dis. 21: 111–157, 1943.
228. Street, H. R., Cowgill, G. R. and Zimmermann, H. M.: Some observations of vitamin B₁ deficiency in the dog. J. Nutrit. 21: 275–290, 1941.
229. Street, H. R., Zimmerman, H. M., Cowgill, G. R., Horr, H. E. and Fox, J. O.: Some effects produced by long-continued subminimal intakes of vitamin B₁. J. Biol. Med. 13: 293–308, 1941.
230. Sure, B.: Amino-acids in nutrition. III. Is proline a growth limiting factor in the proteins of peas (vicia sativa). J. Biol. Chem. 46: 443–452, 1921.
231. Swank, R. L.: Avian thiamin deficiency: A correl[illegible] pathology and clinic behavior. J. Exp. Med. 71: 683–702, 1940.
232. Swank, R. L. and Prados, M.: Avian thiamine [illegible]ologic change in the brain and cranial nerves (especially the [illegible] relation to the clinical behaviour. Arch. Neurol. Psychiat., [illegible]
233. Sydenstricker, V. P. and Armstrong, E. S.: A [illegible]ed and forty cases of pellagra. Arch. Int. Med. 59: 883–891, [illegible]

234. SYDENSTRICKER, V. P. AND CLECKLEY, H. M.: Effect of nicotinic acid in stupor, lethargy and various other psychiatric disorders. Amer. J. Psychiat. **98**: 83–92, 1941.
235. SYDENSTRICKER, V. P., GEESLIN, L. E., TEMPLETON, C. M. AND WEAVER, J. W.: Riboflavin deficiency in human subjects. J. Amer. Med. Assn. **113**: 1697–1700, 1939.
236. TAYLOR, F. R. AND WOOD, E. J.: *Pellagra*. Chap. XIII, Vol. 4. *Oxford System of Medicine*, ed. H. Christian. New York, Revised 1929, Oxf. Univ. Press.
237. TEPLEY, L. J., STRONG, F. M. AND ELVEHJEM, C. A.: The distribution of nicotinic acid in foods. J. Nutrit. **23**: 417–423, 1942.
238. TILLMAN, A. J. B.: Two fatal cases of hyperemesis gravidarum with retinal hemorrhages. Amer. J. Obstet., Gynecol. **27**: 240–247, 1934.
239. TINEL, J.: *Le Système Nerveux Végétatif*. Paris, 1937, Masson et Cie.
240. TONNINI, S.: Sui disturbi spinali nei pazzi pellagrosi. Riv. Sper. Freniat. Med. Leg. **9**: 118–120, 208–236, 429–448, 1883. **10**: 63–72, 1884.
241. TRABAUD, J.: Etude clinique du lathyrisme syrien. Rev. médecine **13**: 439–440, 1932.
242. TUCZEK, F.: Ueber die nervösen Störungen bei der Pellagra. Dtsch. med. Wschr. **14**: 222–225, 1888.
243. TURNER, J. W. A.: Optic atrophy associated with pernicious anaemia. Brain **63**: 225–236, 1940.
244. VEDDER, E. B.: *Beriberi*. New York, 1913, Wm. Wood & Co.
245. VEDDER, E. B.: *Beriberi*, Chap. XII, Vol. VI of *Oxford System of Medicine*, ed. by H. Christian, New York, 1936 Revision, Oxford Univ. Press.
246. VEDDER, E. B.: The pathology of beriberi. J. Amer. Med. Assn. **110**: 893–896, 1938.
247. VEDDER, E. B.: Beriberi or inanition. Amer. J. Trop. Med. **18**: 477–481, 1938.
248. VEDDER, E. B.: Beriberi and vitamin B_1 deficiency. Amer. J. Trop. Med. **20**: 625–640, 1940.
249. VEDDER, E. B. AND CLARKE, E.: A study of polyneuritis gallinarum: A fifth contribution to the etiology of beriberi. Philippine J. Sci. **7B**: 423–461, 1912.
250. VIDAL, E.: Acrodynie. *Dict. Encyclopédique des Sciences Médicales* **1**: 654–663, 1864.
251. VINSON, A.: Du barbiers et du béribéri. L'Union méd., Paris, **9**: 181–191, 1870.
252. WAISMAN, H. A., MCCALL, K. B. AND ELVEHJEM, C. A.: Acute and chronic biotin deficiencies in the monkey (Macaca mulatta). J. Nutrit. **29**: 1–12, 1945.
253. WALSHE, F. M. R.: On the "deficiency theory" of the origin of beri-beri in the light of clinical and experimental observations on the disease, with an account of a series of forty cases. Quart. J. Med. **11**: 320–338, 1918.
254. WARING, E. J.: Notes on the affection called "burning of the feet." Madras Quart. J. Med. Sci. **1**: 300–306, 1860.
255. WERNICKE, C.: *Lehrbuch der Gehirnkrankheiten für Aerzte und Studierende*. p. 229–242, Kassel, 1881, Theodor Fischer.
256. WHALEY, E. M.: Eye symptoms in pellagra. Trans. Nat. Conf. Pellagra, Colombia S. C. **1**: 279–283, 1909.
257. WHITACRE, F. E.: American civilians in a Japanese internment camp. J. Amer. Med. Assn. **124**: 652–653, 1944.
258. WILKINSON, P. B.: Deficiency diseases in Hong-Kong. Lancet, Lond. **2**: 655–658, 1944.
259. WILKINSON, P. B. AND KING, A.: Amblyopia due to a vitamin deficiency. Lancet, Lond. **1**: 528–531, 1944.
260. WILLIAMS, E. D. H.: Discussion on nutritional retrobulbar neuritis. Proc. Roy. Soc. Med., Lond. **39**: 249, 1946.
261. WILSON, S. A. K.: The pathology of pellagra. Proc. Roy. Soc. Med., Lond. **7**: (Section Neurology 31–41), 1944.
262. WINANS, H. M.: Vitamin B1 deficiency in women: Change of voice as a symptom. Tri. State Med. J. **13**: 2723–2725, 1941.

263. Winkelman, N. W.: Beitrage zur Neurohistopathologie der Pellagra. Zschr. ges. Neurol. Psychiat. 102: 38–55, 1926.
264. Wintrobe, M. M., Follis, R. H., Miller, M. H., Stein, H. J., Alcayaga, R., Humphreys, S., Suksta, A. and Cartwright, G. E.: Pyridoxine deficiency in swine, with particular reference to anemia, epileptiform convulsions and fatty liver. Bull. Johns Hopk. Hosp. 72: 1–25, 1943.
265. Wintrobe, M. M., Miller, J. L. and Lisco, H.: The relation of diet to the occurrence of ataxia and degeneration in the nervous system of pigs. Bull. Johns Hopk. Hosp. 67: 377–405, 1940.
266. Wintrobe, M. M., Miller, M. H., Follis, R. H. and Stein, H. J.: What is the antineuritic vitamin? Trans. Assn. Amer. Physicians 57: 55–59, 1942.
267. Wintrobe, M. M., Miller, M. H., Follis, R. H., Stein, H. J., Mushatt, C., and Humphreys, S.: Sensory neuron degeneration in pigs: IV. Protection afforded by calcium pantothenate and pyridoxine. J. Nutrit. 24: 345–366, 1942.
268. Wintrobe, M. M., Mitchell, D. M. and Kolb, L. C.: Sensory neuron degeneration in vitamin deficiency. J. Exper. Med. 68: 207–220, 1938.
269. Wintrobe, M. M., Mushatt, C., Miller, J. L., Kolb, L. C., Stein, H. J. and Lisco, H.: The prevention of sensory neuron degeneration in the pig, with special reference to the rôle of various liver fractions. J. Clin. Invest. 21: 71–84, 1942.
270. Wintrobe, M. M., Stein, H. J., Miller, M. H., Follis, R. H., Najjar, V. and Humphreys, S.: A study of thiamine deficiency in swine. Bull. Johns Hopk. Hosp. 71: 141–162, 1942.
271. Wolbach, S. B. and Bessey, O. A.: Vitamin A deficiency and the nervous system. Arch. Path., Chic. 32: 689–722, 1941.
272. Wolbach, S. B. and Bessey, O. A.: Tissue changes in vitamin deficiencies. Physiol. Rev. 22: 233–289, 1942.
273. Woltman, H. W.: Brain changes associated with pernicious anemia. Arch. Int. Med. 21: 791–843, 1918.
274. Wood, A. J.: Erythroedema. Med. J. Australia 1: 145–148, 1921.
275. Wood, E. J.: *A Treatise on Pellagra.* New York, 1912, D. Appleton Co.
276. Wright, E. J.: Vitamin A deficiency. Brit. Med. J. 2: 234, 1934.
277. Wright, E. J.: Polyavitaminosis and asulphurosis. Brit. Med. J. 2: 707–712, 1936.
278. Wright, H.: Changes in the neuronal centres in beri-beri neuritis. Brit. Med. J. 1: 1610–1616, 1901.
279. Wright, H.: *On the Classification and Pathology of Beri-beri.* London, 1903, John Bale Sons and Danielsson.
280. Wright, H.: The etiology and pathology of beri-beri. Brit. med. J. 2: 1095–1098, 1905.
281. Wyllie, W. G. and Stern, R. O.: Pink disease; its morbid anatomy with a note on treatment. Arch. Dis. Child. 6: 137–156, 1931.
282. Yamaoiva, K.: Beiträge zur Kenntniss der Kakke (Beriberi). Virchow's Arch. path. Anat. 156: 451–506, 1899.
283. Yamaouchi, H.: Zentralskotom bei Beribori (Kakke). Klin. Monatsbl. Augenheilk. 47 (1): 517–520, 1909.
284. Yamamoto, Y.: Ueber Centralskotom bei Kakke. Ophthal. Klinik, Stuttgart, 7: 119, 1907.
285. Young, T. C. M.: A field study of lathyrism. Indian J. Med. Res. 15: 453–479, 1927.
286. Zimmerman, H. M.: Pathology of vitamin B group deficiencies. Proc. Ass. Res. Nerv. Ment. Dis. 21: 13–28, 1943.
287. Zimmerman, H. M., Cowgill, G. R., Bunnell, W. W. and Dann, M.: Studies on the nervous system in deficiency diseases: Experimental blacktongue. Amer. J. Physiol. 109: 440–446, 1934.
288. Zimmerman, H. M., Cowgill, G. R. and Fox, J. C.: Neurologic manifestations in vitamin G (B_2) deficiency. Arch. Neurol. Psychiat., Chic. 286–304

THE CLINICAL DETECTION OF THE GENETIC CARRIERS OF INHERITED DISEASE[1]

JAMES V NEEL, PH D , M D

From the Heredity Clinic, the University of Michigan, Ann Arbor, Michigan

CONTENTS

I. INTRODUCTION

The desirability of being able to detect on clinical grounds the genetic carriers of inherited disease is generally recognized Such detection may shed new light on the physiology of the disease and gene action concerned, by making available for study a relatively large number of individuals who show only slight departures from the norm From the more practical standpoint, this detection can in some instances be a major step in the early diagnosis and treatment of inherited disease, and in other instances a prerequisite to the genetic control of such disease, when and if that control becomes appropriate. It is the purpose of the present review to bring together and evaluate the available literature on this

[1] This study has been largely supported by research grants from the Board of Governors of the Horace H Rackham School of Graduate Studies of the University of Michigan

subject. This literature is widely scattered throughout the scientific publications of the world, and undoubtedly there will be errors of omission in what follows.[2]

At the outset it is necessary to define the term "genetic carrier". Two classes of people transmit inherited disease to their progeny: a) those who actually have the disease, and b) those who appear normal, but whose genetic constitution includes determiners for the disease in question, which determiners for various reasons—environmental factors, dominance relations, etc.—fail to find expression. In the broad sense, "genetic carriers" are those individuals included in the latter group, who may transmit an inherited disease to their progeny without themselves showing *at the time* the commonly accepted findings of the disease. The carriers of the majority of inherited diseases cannot at present be identified clinically, and are known only through the results of a progeny test. However, the transmitters of certain inherited diseases exhibit minor departures from the norm which make it possible to identify them clinically with varying degrees of certainty, depending on the particular disease involved. It is with the detection of these latter individuals that we are here concerned. The possible recognition of carriers through the genetic linkage of the gene responsible for a disease under study with some other easily detected gene, such as those responsible for the A-B-O agglutinogens, the Rh factors, etc., will not be considered.

For each of the diseases to be discussed the following questions must come under scrutiny:

1) Is the disease inherited?
2) What is the most probable mode of inheritance?
3) By what characteristics may the carriers be recognized?

In any case, questions 1 and 2 will be dealt with briefly, since they are covered in reviews and standard works on heredity in man, and attention focussed on 3.

Many of the genes known in man are pleiotropic in their effects, with, in some cases, considerable variability in the manifestation of each of the different effects of the gene. Thus, in Marfan's disease (arachnodactyly) it is very probable that a single dominant factor determines congenital subluxation of the lens, a characteristic elongate body build, congenital heart disease, etc., but there is great variability in the degree of expression of the characteristics. Some individuals show only eye anomalies, while in others the typical habitus is obvious but the eye anomalies very minor. The term "genetic carrier" is not used in this review to include individuals showing only one of the various effects of a dominant pleiotropic gene but capable of producing offspring showing the full syndrome. Actually, of course, such individuals are in a sense carriers, and the distinction artificial.

For convenience in considering the subject material, and not with any thought of setting up a really valid classification based on etiology, the various diseases to be discussed have been grouped as shown in the table of contents.

[2] Since this manuscript went to press, Gates' (75a) extensive compilation of the literature on human genetics has appeared. References to several additional diseases in which a carrier state may probably be recognized will be found there.

II. DISEASES FOR WHICH A CARRIER STATE EXISTS

A. *Metabolic disorders*

1. *Gout* is a disorder of uric acid metabolism characterized chiefly by hyperuricemia; acute and recurring attacks of painful arthritis; tophaceous deposits of sodium urate crystals in articular, periarticular, and subcutaneous tissues; and, in the later stages, vascular lesions, and renal lesions with nephrolithiasis. At least 90 % of affected persons are males. The familial nature of the condition was recognized by the Ancient Greeks. The disease appears to be more common in England than in the United States, although this is a debatable point, and the discrepancy may depend on different standards of diagnosis. In six studies in England between 1819 and 1938 there was gout in the near relatives of patients in 38–81% of the cases (193, 73, 102, 136, 134, 92), whereas in five series in the United States between 1902 and 1946 the percentage of positive family histories was 6–18 (70, 249, 155, 39, 138). The differences in the results of studies on U. S. and English material are consistent with the more frequent diagnosis of gout in England; the chronology of these studies may also be a factor in the differences. Ebstein (quoted from 15) and Garrod (74) have suggested that the condition is inherited as if due to a dominant factor with variable expression, and Garrod in addition first suggested the value of blood uric acid determinations on relatives of patients with gout.

Shortly after the development of quantitative methods for determining the uric acid content of the blood, Folin and Dennis (68) reported a hyperuricemia in a "normal man, many members of whose family had been gouty". Jacobson (103) studied a son of each of two men with clinical gout and a brother of a third patient; all of these persons had elevated blood uric acids. The most extensive reported investigation of this matter has been by Talbott (225), who studied 136 non-gouty relatives of 27 patients with gout. Thirty-four of these relatives, 80% of them males, had hyperuricemia (level greater than 6 mgm.%). The age of the persons with the elevated levels ranged from 14 to 86 years. The exact relationship of the persons with the elevated levels to the patients is unfortunately not given in this paper, but in the two pedigrees which were published, all of the individuals with hyperuricemia had a parent with similar findings, whenever the parents were studied.

Smyth and Freyberg (203) have reported similar findings in a study of two gouty kindreds. The data which they published are only a portion of a more extensive (unpublished) study on heredity in gout which they carried out. These data have been analyzed from the genetic standpoint by Dr. C. W. Cotterman, and I am kindly permitted to quote the results of this work by these investigators. A total of 89 relatives of gouty individuals was studied. When the uric acid levels of males and females were plotted separately, a bimodal curve of distribution was apparent for each sex. The first peak of this curve almost coincided in the two sexes, being 3.5–4.0 mgms.% in the females, and 4.0–4.5 mgms.% in the males, but whereas in the females the second peak was at 5.5–5.9 mgms.%, in males the second peak was less sharply defined but defi-

nitely farther to the right, at around 7.0–8.0 mgms.%. The interpretation placed on this finding was that the genetic factor responsible for hyperuricemia which is present in some of these relatives results in a lower mean uric acid level in females than in males, i.e., there is a difference in the expression of this factor in the two sexes. Of the male parents, siblings, and children of gouty patients, hyperuricemia (greater than 6 mgms.%) was present in 12 out of 29. Of the female parents, siblings, and children of gouty individuals, hyperuricemia (greater than 5 mgms.%) was present in 8 out of 21. In view of the variability of uric acid levels even in gouty patients, this represents a satisfactory approximation to a 1:1 ratio. In every instance where both parents of a hyperuricemic individual were studied, at least one parent showed a hyperuricemia. These observations, and the data in the literature, can most readily be interpreted by assuming that hyperuricemia is due to a single dominant factor of high, although probably incomplete, penetrance. The factor is expressed differently in the two sexes, with heterozygous males having on the average higher uric acid levels than heterozygous females. A possible explanation of the greater incidence of clinical gout in males than in females is that this disease tends to develop in those persons of either sex whose mean uric acid levels exceed a certain value for a certain period, and since hyperuricemic males tend to have higher absolute values than hyperuricemic females, more males than females have gout. The carriers are those individuals with the postulated dominant, and hence hyperuricemia, who do not develop, or have not yet developed, gout.

Bauer and Klemperer (16) have suggested that two coexisting factors are necessary to explain the biochemical alterations in gout, first, a diminution of the uric acid concentrating power of the kidney and second, the presence of a local change in certain tissues which induces precipitation of sodium urate. It may be that the second of these factors is absent in the carrier.

The chief conditions involved in the differential diagnosis are renal disease and diseases associated with an increased purine metabolism (luekemia, pernicious anemia in remission, etc.) (232, 22, 25).

2. *Diabetes mellitus* is a metabolic disorder due to relative or absolute insulin deficiency and characterized by the inability of the body to utilize carbohydrate in the usual manner, with consequent hyperglycemia and glycosuria. The importance of heredity in the etiology of the condition was early apparent from the high incidence of positive family histories, and has been repeatedly reviewed (30, 15, 257, 144, 177, 178, 108, 119, 212, 109, 228). Attempts at analysis are hampered, as in so many diseases, by the variable age of onset of the disease, the death of some persons before the age of possible incidence, uncertainties of diagnosis in preceding generations, etc. In an attempt to overcome these difficulties, Pincus and White (177, 178) have developed appropriate statistical techniques, and through the application of these arrive at the conclusion that diabetes mellitus is inherited as if due to a mendelian recessive factor of low penetrance. It is important to point out that in their treatment of the problem they adopt a unitarian hypothesis of the etiology of diabetes mellitus, a point of view open to some debate. Allan (4) has also suggested a recessive mode of inheri-

tance. Levit and Pessikova (131), on the other hand, adopt the hypothesis that the disease is due to a dominant factor with irregular expression. Many authors regard some pedigrees of diabetes as typical of recessive inheritance, but feel that there is also a dominant type, which is frequently less severe clinically than the recessive type (30, 15, 257, 144, 119). Hansen (88) has suggested a multifactorial basis for the disease.

The possibility of detecting asymptomatic carriers of the condition first emerged from the investigations of Dounevitch in 1916 (quoted from 119) who observed abnormal glucose tolerance curves in the relatives of diabetics; a detailed account of this work has not been available. Allen and Mitchell (6), studying a sibship in which there occurred a high incidence of diabetes, found one asymptomatic person with an abnormal glucose tolerance curve, whom they regarded as having "incipient diabetes." Sherrill (195) performed glucose tolerance tests on 38 apparently normal parents, siblings, and offspring of 23 diabetic patients. The tolerances of about half (55.3%) of these relatives were abnormal by the author's standards. However, the exact significance of these findings is somewhat obscured by the results of control studies. While it was not clearly stated, it appears that 28 persons not under the suspicion of diabetes, and with no family history of diabetes, served as controls; 11 of these (39.3%) also had abnormal tolerances. These control figures are probably misleadingly high, since 12 of the 28 controls were hypertensives, and 7 of these 12 had abnormal curves. The unsuitability of hypertensives for controls is suggested by O'Hare's (166) report of abnormal glucose tolerance curves in such individuals.

This finding, of an increased incidence of abnormal glucose tolerance tests in the apparently normal relatives of diabetics, has been confirmed by many investigators (105, 194, 67, 131, 179, 171, 212, 107) but questioned by some (85, 143). The results of the various investigations are summarized in table 1. A fact which emerges clearly is that aside from the early work, there has been only one investigation in which control studies were carried out. In this, Pincus and White (179) found that of 76 "relatives" (exact relationship not specified) of diabetics, 11 (14.5%) had fasting blood sugar levels higher than any observed in an equal number of controls. Glucose and sucrose tolerance tests were performed on an additional 95 "relatives" of diabetics, of whom 19 (20%) showed abnormally high values during at least one of the three ($\frac{1}{2}$, 1, and 2 hour) observations. In a control series of 49 persons, an abnormally high value was encountered only once. Of the total of 171 "relatives" studied, 103 were siblings of diabetic patients. These siblings may be divided into three classes on the basis of parental diabetes, as follows: 1) both parents diabetic, 2) one parent diabetic, and 3) neither parent diabetic. Five of 20 siblings (25%) from the first group, seven of 39 class 2 siblings (17.9%) and three of 44 class 3 siblings (6.8%) showed hyperglycemia either on a single fasting determination or a glucose tolerance test.

It is apparent from table 1 that the results of Greisheimer and Goldsworthy (85) are in contrast to the bulk of the reported work. They studied a total of 96 relatives of diabetics. An attempt was made to standardize the diet for a

short time prior to the test — a precaution that has generally been neglected. It was concluded that "no abnormalities appear constantly in the glucose tolerance in subjects who have maternal diabetic relatives, paternal diabetic relatives, diabetic relatives in the two preceding generations, or in those who have both maternal and paternal diabetic relatives."

TABLE 1

The occurrence of abnormal carbohydrate tolerances in relatives of diabetics

INVESTIGATOR	RELATIONSHIP OF SUBJECTS TO DIABETICS	TYPE OF TEST	NO.	RESULTS: % ABNORMAL	CONTROLS	RESULTS: % ABNORMAL
Sherrill (195)	parents, siblings, and children	glucose tolerance	38	55.3	28	39.3
John (105)	family history of diabetes	glucose tolerance	104	55.7	287	25.8
Sehestedt (194)	siblings	glucose tolerance	6	50.0	—	—
Flaum and Schlesinger (67)	diabetic parent, or two or more diabetic relatives	glucose tolerance	32	72.0	—	—
Levit and Pessikova (131)	"near relatives"	glucose tolerance	40	10.0	—	—
Pincus and White (179)	"relatives"	fasting blood sugar	76	14.5*	76	0.0
	"relatives"	glucose and sucrose tolerance	95	20.0	49	2.0
Mackler and Fischer (143)	siblings (mostly children)	glucose tolerance	30	0.0†	—	—
Greisheimer and Goldsworthy (85)	"relatives"	glucose tolerance‡	96	0.0§	—	—
Pannhorst (171)	? children and grandchildren of conjugal diabetics	glucose tolerance	26	42.3	—	—
Steiner (212)	parents, siblings, and children	glucose tolerance	258	11.3	—	—
Jonas (107)	"relatives"	glucose tolerance	100	54.0	—	—

* 14.5% of the relatives of diabetics had a blood sugar level higher than any observed in the controls.

† 5 children gave abnormal values on the initial observation, but were normal when retested 6 years later.

‡ Attempted to place subjects on a short period of standardized diet prior to testing.

§ "No abnormalities appear constantly in the glucose tolerance in subjects who have maternal diabetic relatives, paternal diabetic relatives, diabetic relatives in the two preceding generations, or in those who have both maternal and paternal diabetic relatives."

The results of Mackler and Fischer (143) also warrant special consideration. They studied the glucose tolerance curve in 30 siblings of juvenile diabetics. Three of those examined gave a relatively high value at the 1-hour reading, and two, in addition to high values at the 1-hour determinations, also had ele-

vations at the 1½-hour determinations. However, when these five children were retested six years later, their curves were normal. For this reason the authors are inclined to doubt the significance of these abnormal curves from the standpoint of their relation to the future development of diabetes in children.

As one aspect of an extensive investigation, Steiner (212) studied the glucose tolerance curves of 258 parents, siblings, and children of diabetic patients, finding that 3.5% of these showed "latent" diabetes, and 7.8% lesser abnormalities in the carbohydrate utilization. Lemser (120) reported the results of follow-up studies on six of Steiner's "latent" diabetics, and 16 of the individuals in whom Steiner had detected lesser abnormalities of the curve. A period of three and one-half years elapsed between the observations of the two investigators. In this interval, two of the six "latent" diabetics had developed clinical diabetes, and one of the 16 with lesser abnormalities was now classed as a "latent" diabetic. These studies are of especial value in that, together with the above quoted work of Mackler and Fischer (143) and a single case quoted by Sehestedt (194), they constitute the only follow-up studies on these individuals with abnormal glucose tolerance curves. Lemser (120) also reported on a German family of 12 children, the offspring of two diabetic parents. Five of them were stillbirths, died in infancy, or were killed in World War I. Three had developed clinical diabetes at the time of the report. Three of the four remaining children could be located for a carbohydrate tolerance test—all three were thought to show somewhat abnormal curves.

Then Bergh (228) has carried out extensive observations on diabetes in twins. Of particular interest in the present connection is that of 36 identical twin pairs of whom at least one was diabetic, both were diabetic in 17 instances, and one diabetic but the other with an abnormal glucose tolerance curve in 13 pairs. In 23 pairs of fraternal twins, both were diabetic in two instances, and one diabetic and the other with an abnormal glucose tolerance in seven pairs. Both types of twins, especially the identicals, thus give evidence for a genetic association between outspoken diabetes and abnormal tolerance curves.

In summary, it is obvious that there is a significant discrepancy between the results of various investigators. Part of the difference is due to varying standards of what constitutes an abnormal glucose tolerance curve and different modes of administration of the test carbohydrate. However, the discrepancy seems greater than can be accounted for on this basis alone. Most of these investigations have been poorly controlled, and the relatives investigated in all these studies have only rarely had the preliminary period of standardized diet now recognized as an important factor in the performance of carbohydrate tolerance tests, especially where relatively small departures from normal are involved. Be that as it may, the bulk of the work indicates that not only is there an increased incidence of clinical diabetes among the relatives of diabetics, but also an increased incidence of abnormal glucose tolerance tests in the apparently normal relatives of these same diabetics. An unspecified proportion of individuals with such abnormal curves may develop clinical diabetes later; there is little exact evidence on this point. However, another unspecified proportion may possibly remain stationary but transmit tendencies to abnormal sugar

metabolism to their offspring. Regardless of the ultimate clinical fate of these individuals, they would appear to be detectable carriers of the disease.

The chief problem in differential diagnosis is probably in distinguishing carriers from those individuals who show minor elevations in their curves because of previous low carbohydrate diets. This difficulty can readily be eliminated by the preliminary administration of a standard, high-carbohydrate diet. Disease states to be considered include hyperpituitarism, hyperthyroidism, chronic infection, cerebral lesions, hypertension, and liver damage (especially an acute, diffuse process). Nephritis, arthritis, and pregnancy are also reported to be associated with abnormal tolerances (232, 108, 22, 25).

3. *Primary essential xanthomatosis* is a disease (or collection of diseases) characterized by a disturbance in lipid metabolism. There are several distinct types. The usually accepted classification is that of Thannhauser and Magendantz (227), who on the basis of the cholesterol content of the blood and the clinical picture draw the distinction between a hypercholesterolemic and a normocholesterolemic type. The former is associated with a tendency to xanthomatous involvement of the skin, tendons, cardiovascular system, liver, pancreas, etc., resulting in disfiguring skin lesions (xanthoma tuberosum), tendon tumors, and—more serious—early cardiovascular and hepatic disease. The normocholesterolemic type is frequently associated with a different variety of skin lesion (xanthoma disseminatum) as well as osseous involvement. The condition has been the subject of many communications since its description in 1850 by Addison and Gull (1), including several excellent reviews touching on the genetic problems involved (239, 227, 226, 114, 21). The nature of the primary metabolic defect is still obscure, but Thannhauser and Magendantz (227) have made a strong case for regarding this condition, like Gaucher's disease and Nieman-Pick's disease, as being primarily an intracellular disturbance of lipid metabolism. The hypercholesterolemia is regarded as a secondary phenomenon.

The hypercholesterolemic is the more common type, and the type referred to in the following discussion. The condition is usually thought to be rare, although Müller (158) states that "hereditary heart disease due to xanthomatosis is fairly common," and Engelberg and Newman (61) regard it as a significant cause of heart disease in the relatively young. The relation of this condition, in a mild and unrecognized form, to the problem of arteriosclerosis and arteriosclerotic heart disease is a challenging question.

Although Wilks (quoted by 62) observed xanthoma tuberosum in a mother and her daughter, Török (230) was apparently the first to emphasize the hereditary nature of the disease. Gossage (82) in 1908 pointed out that the ratio of normal persons to those with xanthoma tuberosum in the families that had been reported up to that time approximated 1:1, and that the condition was usually "directly inherited," although occasionally unaffected persons transmitted the disease. Fasold (64) in a later summary of the literature found that in nine out of 33 families the parents of the affected patients were free of cutaneous lesions, but that there was often an affected grandparent or great-grandparent, and suggested an irregular dominance.

The discovery that many of these apparently normal transmitters of the disease, as well as some of the apparently normal siblings of patients, have elevated blood cholesterol values even though there are no skin lesions suggests that the apparent irregular dominance is true chiefly with regard to the cutaneous and tendon lesions, and that in a great many of these apparently normal transmitters the basic disturbance is nonetheless present (190, 117, 91, 116, 207). We may therefor recognize as carriers of this disease those individuals who have hypercholesterolemia but show none of the commonly recognized clinical manifestations of the condition, i.e., the cutaneous and tendon lesions which are synonymous in the minds of most physicians with xanthomatosis. Some of these carriers, the younger, may be expected to develop cutaneous xanthomatous deposits in time; others may never show such lesions, and yet develop heart or liver disease later—the "forme fruste" (227)—and transmit the same tendencies to their children. There is reason to believe that in some families only a fraction of the persons with the fundamental metabolic defect (as manifested by hypercholesterolemia) develop the superficial xanthomatous deposits that are usually the clue to the diagnosis (239, 220).

Therapy in this disease consists in placing affected persons on a low cholesterol diet, a treatment which is soon followed by a drop in blood cholesterol (239, 91, 71, 191). There have been no extended observations adequate to determine whether this form of therapy really alters the prognosis of the disease. Assuming that the pathological changes will be retarded on a low cholesterol diet, then an incentive to detecting carriers is the possibility, through dietary restrictions, of adding useful years to their lives. The same consideration applies to diabetes and gout, although the efficacy of dietary restrictions in the control of the latter is also a matter for debate.

Other possible states which have been reported to be associated with hypercholesterolemia—diabetes, hypothyroidism, nephritis and nephrosis, pregnancy, obstructive and hepatogenous jaundice—must of course be excluded in reaching the diagnosis (232, 22, 25).

B. Diseases of the nervous system

1. *Epilepsy* is a chronic disorder characterized by sudden loss of consciousness, which may be only momentary, or which may be prolonged and accompanied by a convulsion. There exist many variants of the disease. Recently, considerable attention has been directed towards the so-called epileptic *equivalents*, these consisting of mental states characterized by amnesia, automatism, periods of excitement, etc. The disorder may be related to syphilis, cerebral neoplasm, trauma, etc., but more often it is "idiopathic." It is primarily with this latter category that we are here concerned, although the difference between "idiopathic" and "secondary" epilepsy is frequently not clear cut—if, indeed, there always is a valid distinction. From the reviews dealing with the inheritance of this trait (23, 24, 15, 210, 172, 121, 75), it appears that about 25–30% of epileptics have a family history of this disorder. The exact proportion varies considerably from series to series, depending on the investigator's thoroughness and criteria

Otherwise put, seizures are five to six times more frequent in the parents, siblings, and children of epileptics than in the general population. If one of identical twins is epileptic, the other is also in 70% of cases.

The development of the electroencephalogram opened a new chapter in the study of heredity in epilepsy. In 1933 Berger (18) demonstrated the abnormal nature of the electroencephalogram in epileptics, an observation soon confirmed by many investigators (esp. 77). Four years later Lennox, Gibbs, and Gibbs (125), Löwenbach (135), and Strauss, Rahm, and Barrera (216) independently described the occurrence of abnormal brain waves in some of the clinically asymptomatic parents, siblings, and children of patients with epilepsy. The eugenic significance of these findings was quickly recognized (126). Since 1939 there has been a veritable flood of literature on the electroencephalogram in epilepsy, including a number of reviews touching on the genetical aspects of the problem (28, 122, 123, 78, 80, 76). Of especial interest are the observations on twins, to the effect that in seven identical twin pairs where only one member showed epilepsy, the other showed a significant cerebral dysrrhythmia in every case, although in most instances the disorder was not as pronounced or localized as in the patient (127). From the study of twins it was concluded that the EEG furnishes "presumptive evidence that epilepsy per se is not inherited but that cerebral dysrrhythmia is inherited and that this genetic factor combines with acquired factors to produce seizures" (128).

Lennox (124) has recently summarized the findings of his group in two succinct tables:

a) *Classification of electroencephalograms of 1000 controls, 470 near relatives of epileptics, and 780 adult epileptics.*

ELECTROENCEPHALOGRAM	PER CENT OF CONTROLS	PER CENT OF RELATIVES	PER CENT OF EPILEPTICS
Normal	84.2	49.5	16.3
Mildly slow or fast	13.8	36.4	32.4
Very slow or fast	1.1	6.6	22.0
Seizure discharges	0.9	7.0	29.3
	100.0	100.0[3]	100.0

b) *Electroencephalograms of parents of 140 epileptics.*

	PER CENT
Both normal	18.6
One normal, other mildly slow or fast	43.5
One normal, other very slow or fast	9.3
One normal, other with seizure discharges	5.0
Both mildly slow or fast	12.8
One mildly, other grossly abnormal	7.3
Both grossly abnormal	3.5
	100.0

[3] This column fails to total to 100%. The error is present in the original.

A number of very significant facts emerge from these two tables. Thus, an abnormal EEG is not always present in epilepsy, and conversely, in a random sample of the population many individuals who have never given any indications of epileptic tendencies will have abnormal brain waves indistinguishable from those observed in epilepties. An EEG is like any other laboratory procedure, to be considered in the light of the clinical findings. In 84.1% of the families studied at least one parent, and in 23.6% of the families both parents, showed an abnormal EEG. This fact assumes added significance when it is recalled that only 83.7% of epilepties have abnormal brain waves. The obvious conclusion is that the "carriers" of epilepsy may often be detected by a study of brain waves, although not all persons with abnormal brain waves are necessarily transmitters of the disease, and some individuals who are normal in this respect, including even some epilepties, should probably be regarded as transmitters. The frequency (23.6%) with which both parents are affected suggests that in some cases the susceptibility to seizures depends on a genetic contribution from both parents. It may be that a careful clinical study of patients from the standpoint of the abnormality of their brain waves in relation to the abnormalities present in the parents will lead to a clearer clinical classification of epilepsy.

2. *Phenylpyruvic amentia* (Phenylketonuria) is a rare disease characterized by amentia, usually on the idiot or imbecile level and the excretion of phenylpyruvic acid in the urine. The condition was first recognized by Fölling (69) and soon confirmed by Penrose (173). The exact relation between the metabolic abnormality as revealed by studies of the urine and the mental condition is not known.

Fölling's original ten cases included three pairs of siblings, so that a probable hereditary factor was apparent from the first. The first two cases reported by Penrose (173) occurred in brothers, and he suggested that the disease was due to a single Mendelian recessive factor. Later Penrose (174) published a pedigree covering five generations and including four individuals probably affected with the disease. In this same pedigree there were six relatives who showed definite signs of insanity, with the mean age of onset about 50 years. Three of these were certainly heterozygotes, two had a 2:1 chance of being heterozygous, and one had an even chance of being heterozygous. It was suggested that the heterozygotes show a marked tendency to develop insanity in the involutional period of life, and that such heterozygotes might contribute a significant proportion to the insane individuals in the general population. The insanity was in no way characteristic. Jervis (104) and Fölling, Mohr, and Ruud (quoted from 175) have confirmed the recessive nature of the disease, but despite an extensive material have been unable to establish a definite increase in the incidence of insanity in the heterozygotes.

The extensive studies of Sjögren (199) on juvenile amaurotic idiocy raise the possibility that in this disease, which likewise appears to be inherited as a recessive trait, the heterozygous carriers also show an increased incidence of mental disorders.

C. *Disorders of the blood*

1. *Thalassemia* (Cooley's anemia) is a chronic, fatal, progressive anemia of childhood characterized by a hypochromic, microcytic anemia, peripheral erythroblastosis, splenomegaly, a characteristic mongoloid facies, hyperplasia of the bone marrow resulting in typical X-ray findings, and a familial incidence. Moncrieff and Whitby (154) suggested that the disease was due to a single recessive factor. The disease was first described by Cooley and Lee in 1925 (45). Fifteen years later Wintrobe, Mathews, Pollack and Dobyns (254), Dameshek (50) and Strauss, Daland, and Fox (218) independently described a familial anemia qualitatively similar to that described by Cooley and Lee, but quantitatively very much less severe, without the peripheral erythroblastosis, marked splenomegaly, or characteristic facies, and never terminating fatally. It is possible that the "benign familial polycythemia" described by Spodaro and Forkner (208) was this same entity. Both anemias are largely confined to the so-called Mediterranean peoples—Italians, Greeks, Cypriots, Turks, etc., and their descendants—and are resistant to all known therapeutic measures. Wintrobe (252) observed that the mild anemia was present in both the parents of two children with thalassemia. Smith (200) independently observed the mild anemia in the father and brother of a patient with thalassemia; there were also slight departures from the normal in the mother's blood picture, which at the time were not considered significant. This observation, of the association of the two types of anemias in families, was quickly confirmed and extended (51, 201, 234, 162).

From an analysis of all the available data it becomes apparent that:

1) Whenever they have been subjected to a careful examination, both parents of children with thalassemia have in all cases reported to date shown departures from the normal blood picture which are in some cases slight, but usually unmistakable.

2) The occurrence of thalassemia in sibships shows a satisfactory approximation to a 3:1 ratio.

3) Among those siblings of a child with thalassemia who do not themselves show thalassemia, mildly anemic and normal children occur in a ratio of 2:1.

4) In marriages between normal and mildly anemic persons, normal and mildly anemic children occur in a 1:1 ratio.

These facts can most readily be interpreted (51, 234, 162) in terms of an hereditary factor which when heterozygous produces the mild disease, and when homozygous the severe anemia. Valentine and Neel (234) have suggested that the term thalassemia minor be applied to the mild anemia (the presumptive heterozygote) and thalassemia major to the severe disease (the presumptive homozygote). Thalassemia major has been found from a survey of the Italian element of Rochester, N. Y., which is predominantly of Sicilian and Southern Italian extraction, to occur with a frequency of 0.042% in this group, from which, assuming a population in equilibrium, the frequency of thalassemia minor, the carrier, has been calculated at 4.0% (161). An alternative interpretation of these facts is that thalassemia minor is due to the action of either of two inde-

pendent dominant genes which when present simultaneously in an individual result in thalassemia major (140). For various reasons this hypothesis is less probable than the first described (234, 162).

The carrier can be diagnosed with a high degree of accuracy, where the criteria for diagnosis are:

1) A mild hypochromic, microcytic anemia. In the 70 persons with this condition whom the author has seen, the hemoglobin content of the blood averaged 2.0 ± 0.16 gms. % lower than the commonly accepted values for the given age, where the standard for an adult female was taken as 14 gms. % and for a male, 16 gms. %. Many carriers partially or wholly compensate for their individually deficient erythrocytes by maintaining increased numbers of them in the circulation, with erythrocyte counts of 6-7,000,000/mm.^{3} not being at all uncommon.

2) A decrease in the fragility of erythrocytes in hypotonic saline solutions. This fragility change in parents and siblings was first noted by Angelini (quoted from 254) and Caminopetros (29) who, however, did not recognize the other changes present in the carriers.

3) The appearance of a stained blood smear. There is mild hypochromia and micro-, aniso-, and poikilocytosis. Two cell types are especially characteristic: the ovalocyte and the "target cell." These latter are erythrocytes which instead of the usual achromic center appear to have a central dot and a peripheral ring of hemoglobin separated by an intervening zone of pallor.

4) The elimination of other possible causes of a similar picture—nutritional anemia and chronic blood loss.

5) Failure to respond to any therapy known at present.

6) A familial incidence.

Thalassemia major shows all these features, but the degree of the anemia is much more severe, and erythroblasts are present in the circulation. Other characteristics have been mentioned above. All these changes in both major and minor can be attributed to a defect in erythropoiesis which is more extreme in the homozygote than in the heterozygote. For the present, thalassemia minor may be regarded as the most regularly expressed carrier state known in man. If marriages between carriers were to cease, thalassemia major would disappear in a single generation.

2. *Sickle cell anemia* is a chronic anemia confined almost entirely to negroes and characterized clinically by rheumatoid pains, leg ulcers, hemolytic crises, hyperplasia of the bone marrow with typical X-ray findings, the general symptoms of anemia, and a characteristic hematologic picture. The finding from which the disease derives its name is the occurrence of elongate, pointed, often curved, "sickle"-shaped erythrocytes in the peripheral blood. These may be observed in small numbers on stained smears of fresh peripheral blood, but the frequency can be increased to close to 100% when the blood is treated appropriately, as when a drop of blood is sealed under a cover slip and observed after 24 and 48 hours. Although the disease is predominantly confined to negroes, Wintrobe (252) accepts seven apparently well substantiated cases in whites; significantly

enough, the majority of these cases were in persons of Greek, Southern Italian, or Sicilian stock. The geographical position of these groups has rendered them especially prone to racial admixture with negroes. The literature on the disease has been well summarized by Wintrobe (252) and Lewis (132).

The first observation on the inheritance of the condition was by Emmel (60, 41), who observed in a vaseline-sealed, drop preparation of the blood of the asymptomatic father of a girl with sickle cell anemia, the occurrence of sickle cells. Later Huck (99), Taliaferro and Huck (225a) and Sydenstricker, Mulherin, and Houseal (224), starting with probands with clear-cut sickle cell anemia, were able to trace the occurrence of sickling through three generations. Most of the individuals in their pedigrees whose erythrocytes could be induced to sickle were asymptomatic. They felt that the property of forming sickle cells was inherited as if due to a single dominant factor whose effects varied from the production of a small per cent of sickle cells in asymptomatic individuals to the production of a severe anemia in other individuals, and this is a point of view that has been rather generally accepted.

Since these early studies it has become apparent that there is a difference between the occurrence of sickle cells in the blood after appropriate treatment (sicklemia) and sickle cell anemia. The former is an asymptomatic condition characterized only by the appearance of these bizarre cells in the blood after special treatment, whereas the latter is the disease described above. A compilation of the literature (132) showed that sicklemia occurred in 7.48% of 11, 121 colored individuals studied. These studies were on American negroes. Evan's report (61a) of 19.9% sicklemia in a group of 561 West African natives suggests that the incidence of the trait may be even higher in pure negroes (although see 55), while the findings of Trowell (231) indicate that sickle cell anemia is not uncommon in this group. The ratio of sickle cell anemia to sicklemia in American negroes has been estimated by various investigators as 1:9 (222), 1:9.5 (106), 1:11 (229), 1:40 (55), and 1:50 (Sydenstricker, in discussion to 54). On the other hand, McGavack and German (139) found 8% sickling in 300 Black Carib Indians, but were unable to find evidence that sickle cell anemia ever occurs in this group. The medical relationship between these two conditions has been much debated. At present there are no long term studies showing whether sicklemia ever becomes sickle cell anemia or vice versa, i.e., the possibility exists that the two conditions are to be regarded as largely or wholly distinct (46, 211, 8, 55, 194a, 132, 59). The present interpretation of the data reported by Huck and Sydenstricker would therefore be that a person with sicklemia may have a child with sickle cell anemia.

In a compilation of the available literature on the familial incidence of sickleemia and sickle cell anemia, I have been able to find reports of 31 families in which the bloods of both the parents of a child with sickle cell anemia were studied (224, 99, 221, 9, 86, 17, 213, 256, 202, 223, 47, 189, 42, 10, 113, 243, 169, 115, 168, 142, 156, 165, 19, 32, 231). In some of the early case reports, as, indeed, in a recent review (215), the distinction between sicklemia and sickle cell anemia is not clearly drawn, and in such instances the interpretation of the classification of the members of the family is of necessity the author's. In seven of these families

neither parent had sicklemia, in nine families both parents showed sicklemia, while in fifteen families one parent showed the trait. To these published reports I can add unpublished observations on one family, in which both the parents of a child with sickle cell anemia were found to show sickling.

The absence of sickling in both parents in $\frac{7}{32}$ of the families studied is strong evidence against the commonly accepted hypothesis that sickle cell anemia is due to a single, completely penetrant, dominant factor which produces in some individuals only sickling, and in others a severe anemia. Further evidence of a similar nature is derived from studies of the parents of persons with sicklemia. Here also there are recorded instances where neither parent of a person with sicklemia shows sickling (46, 238). While impaternity and mutation are possibilities that can be invoked to explain a certain number of apparent exceptions, it is unlikely that they could account for all these families with neither parent affected. Two clear-cut alternatives seem open. One is to postulate that from the genetic standpoint there are at least two distinct types of sickle cell anemia, one due to a recessive factor, and one due to a dominant factor. The other is to postulate that the gene responsible for sickling is not always completely dominant but sometimes fails to find any expression at all, i.e., some individuals with this gene are either indistinguishable from normal, or else they have not been studied in such a manner as to bring out the trait. The variability of the sickling phenomenon is well known (83, 7, 84, 132). Thus, in the family studied by the author, a sibling of the patient showed no sickling at 24 or 72 hours, but about 5% at 48 hours. Since in some investigations observations apparently only extended to 24 hours, individuals such as this would be missed. More female (20/32) than male (14/32) parents showed sicklemia, in a proportion that corresponds to the different incidence of sicklemia in the two sexes in one author's large series: males 7.2%; females 11.4% (229). The different incidence in the two sexes, although the trait does not appear to be sex-linked in its inheritance, suggests the importance of modifying influences, which in some cases may completely suppress the expression of the gene.

In approximately a third of the families studied, both parents showed sickling. This is a higher proportion than would be expected on the hypothesis of a variably expressed dominant factor, where the frequency of sickling in the population is only 7.5%, especially if we assume that the sickling gene sometimes fails to find expression. Analogy with the situation which obtains with respect to thalassemia suggests a further modification of Huck's original hypothesis. This is that there is present in the colored population a certain factor which when heterozygous may have no discernible effects but usually results in sickling, and when homozygous tends to result in sickle cell anemia.

Much remains to be done in the way of a careful study of the genetics of this interesting and—to the negro—important disease. Whatever the final answer, the frequent occurrence of sicklemia in the parents of patients with sickle cell anemia provides another example of a carrier relationship.

There is no problem of differential diagnosis in sicklemia, since the finding of sickle cells is pathognomonic.

3. *Congenital hemolytic jaundice* is an uncommon familial disorder character-

ized in most patients by a chronic, low-grade hemolytic anemia with jaundice. The course of the disease is punctuated by hemolytic crises with temporary increase in the degree of the anemia and deepening in the jaundice. Splenomegaly is an almost constant finding. The fundamental defect appears to be either an abnormality in erythropoiesis which results in an increased production of spherocytes, or the existence of an abnormal hemolytic agent or mechanism which converts normal erythrocytes to spherocytes (cf. 49). Such spherocytes are unusually fragile, as is shown by their diminished resistance to hemolysis in hypotonic saline solution. The increased destruction of these abnormal erythrocytes, in which the spleen is thought to take a leading role, accounts for the anemia and the icterus.

Minkowski (152) is usually credited with the first clear-cut description of the disease, although Wilson (250, 251) and Hayem (90) among others described cases of the disease in some detail. From the first a strong hereditary tendency was obvious, Wilson describing six affected persons in a single family, and Minkowski eight. As more pedigrees of the disease were recorded, it was noted that transmission was usually from one affected person to another, suggesting inheritance due to a dominant factor (Plate, quoted from 149). However, occasionally a generation appeared to be skipped. This fact was a stumbling block until Giffen (79) and Gänsslen (72) pointed out that individuals might be clinically completely asymptomatic and still show characteristic changes in the erythrocytes, a fact confirmed in some detail by Campbell and Warner (31). There exists, then, a continuous spectrum of the disease, from clinically asymptomatic to severely affected. The asymptomatic transmitters are carriers of the disease and account for the apparent skipping of generations. In those pedigrees where fragility tests have not been done on all individuals classed as normal, the ratios are open to doubt.

An important question is whether the genetic carriers ever overlap with, and are completely indistinguishable from, normal, i.e., do not even show fragility changes. Unfortunately, most of the data in the literature cannot be used for the exact analysis this question requires, since it is not stated which individual is the proband, what the criteria for diagnosis were, or what the findings were on all individuals studied. The most precise approach to the problem is that of Race (182) who has published the results of studies on 26 families, including 183 persons. Detailed hematologic studies are not included in this paper but are to be given in a separate communication that has not yet appeared. Even after eliminating some possible instances of acquired hemolytic anemia from his data, he finds in the sibships and children of probands a significant departure from the expected 1:1 ratio in the direction of an excess of normals. It is concluded that "the explanation probably lies in the high miscarriage and infant mortality rate in the jaundiced branches of these families, it being likely that there is a disproportionate number of acholurics amongst the dead children. To a less extent limitation of penetrance has probably contributed to the excess of apparently sound sibs."

The chief condition to be considered in the differential diagnosis is an early, asymptomatic acquired hemolytic anemia.

4. *Pernicious anemia* is a chronic disorder usually developing insidiously in late adult life and characterized by a progressive, severe macrocytic anemia accompanied by the usual symptoms of a profound anemia; evidences of increased blood destruction; achlorhydria; and neurological and gastrointestinal symptoms. The accepted hypothesis of the etiology of the condition, developed by Castle and his coworkers (cf. esp. 33) postulates that in normal individuals an extrinsic factor supplied by the diet interacts in the gastrointestinal tract with an intrinsic factor present in the gastric juices to form, probably after appropriate intermediate steps, an anti-anemic factor stored chiefly in the liver. In pernicious anemia the intrinsic factor is deficient, and the anti-anemic principle cannot be formed. The achlorhydria present in persons with pernicious anemia may be regarded as one index of a poorly functioning digestive tract unable to elaborate the intrinsic factor.

Recognition of the hereditary factor in the etiology of pernicious anemia was slow in coming, perhaps because of the special difficulties in studying inheritance in this disease (cf. 150), but is now firmly established. The evidence for the inheritance of a susceptibility to the disease is chiefly of three types: 1) *Case reports of kinships showing multiple occurrences of the disease.* In 1940 Askey (11; see also 40 and 248) was able to locate 235 instances of multiple familial occurrence. These represent selected data but nevertheless contribute legitimate information. 2) *Reports of the familial incidence of the disease in a series of unselected, consecutive cases.* The frequency of occurrence of pernicious anemia in the families of patients with the disease is given by various authors as 8% (160), 9% (246), 16.7% (111) and 7.9% (209). 3) *The occurrence of the disease in identical twins.* Askey (11) was able to find eight reports of probably identical twins involved by the disease: both members were affected in four pairs, one member was involved and the other probably had a "latent" form in three pairs, while for one pair the data were to meager to permit any definite conclusions. Alder (3) has since added a report of another set of identical twins, both affected. There can be little doubt of the tendency of the disease to cluster in certain kindreds, and this is not due to environmental influences because marital partners so far as is known are no more often affected than the population at large.

Although Fenwick (66a) in 1877 pointed out the atrophy of the stomach present in pernicious anemia, the achlorhydria which accompanies the disease was not observed until some years later (38). Evidence that this achlorhydria[4] may precede the appearance of the anemia by many years was first advanced by Lichty (133), and has since been confirmed by numerous observations (tabular summary in 40). The importance of this achlorhydria—or rather, the state of the gastric mucosa which is reflected by the achlorhydria—in the etiology of the disease has been emphasized by Martius (147) and many others since. Especially significant from the standpoint of hereditary factors in the pathogenesis

[4] In the majority of cases of pernicious anemia there is, more properly speaking, an achylia gastrica present (51a). However, many authors in reporting the results of gastric analyses do not distinguish between achlorhydria and achylia, and in this review the more noncommittal term achlorhydria is used.

TABLE 2

The occurrence of achlorhydria and hypochlorhydria in the relatives of patients with pernicious anemia, and in control series

AUTHOR	RELATIONSHIP OF SUBJECTS	NUMBER OF SUBJECTS	AVERAGE AGE	% WITH ACHLORHYDRIA	% WITH HYPOCHLORHYDRIA
Weinberg (241) (no histamine)	siblings children	2	45.0	50.0	0.0
		22	14.0	41.7	29.1
Neuberger (163) (use of histamine not stated)	siblings and children	29	—	3.4	—
Zadek (259) (no histamine)	mostly siblings and children	46	—	21.7	32.6
Wilkinson and Brockbank (248) (no histamine)	siblings	5	39.0	40.0	20.0
	children	29	26.1	20.7	48.3
	parents	1	60.0	100.0	0.0
Conner (40) (no histamine)	parents	7	61.7	42.9	—
	siblings	53	47.4	35.8	—
	children	87	29.5	19.5	—
	spouses	60	49.0	16.7	—
Werner (246) (no histamine)	"near relatives" ($\frac{1}{2}$ and $\frac{1}{4}$)	—	—	19.0	—
	"distant relatives" ($\frac{1}{8}$ and $\frac{1}{16}$)	—	—	9.0	—
Kaufmann and Thiessen (111) (histamine)	parents	8	—	37.5	0.0
	siblings	39	—	17.9	15.4
	children	76	—	14.5	26.3
	more distant	32	—	9.4	9.4
Kiefer and Bloomfield (112) (no histamine)	none (control series)	570	10–19	12.5	—
			20–29	6.0	—
			30–39	6.0	—
			40–49	17.0	—
			50–59	21.0	—
			60–69	36.0	—
			70–	50.0	—
Lerman, Pierce, and Brogan (129) (histamine)	none (control series)	5	–20	0.0	0.0
		23	20–29	4.3	13.0
		40	30–39	12.5	17.5
		40	40–49	10.0	15.0
		51	50–59	19.6	17.5
		36	60–69	16.7	16.6
		5	70–	0.0	40.0
Vanzant et al. (236) (histamine in some)	none (control series)	581	20–29	3.4	—
		790	30–39	6.5	—
		744	40–49	10.9	—
		672	50–59	18.2	—
		455	60–69	25.1	—
		76	70–79	18.4	—

was the discovery that achlorhydria frequently occurred in relatives of patients with pernicious anemia (110, 180, 144, 101, 56), concerning which Hurst (101) wrote: "The familial occurrence of achylia gastrica must be the explanation of

the familial occurrence of Addison's anemia, which has been recorded by many investigators." Table 2 summarizes the findings in several series with respect to the incidence of achlorhydria in parents, siblings, and children of individuals with pernicious anemia, plus control figures. With the exception of Neuberger (163) all the series show an increased incidence of achlorhydria and—where it was studied—hypochlorhydria. However, failure to employ a standard technique, especially with reference to the use of histamine, makes comparison difficult. The tendency to achlorhydria appears to behave as if due to a dominant factor with irregular expression. Whether some of the persons with hypochlorhydria would at a later date develop achlorhydria, resulting in a closer approximation to mendelian ratios, has not been determined.

The blood picture in relatives of patients with pernicious anemia has also been investigated (241, 248, 246, 111), and in some, significant changes, consistent with the first stages of pernicious anemia, have been observed. For example, Werner (246) found a "pre-pernicious anemia" state in 15% of the siblings of outspoken cases. These slight changes are with very few exceptions found in persons with achlorhydria (cf. 111). It is not clear what proportion of these individuals will progress to clinical pernicious anemia, and what proportion remain stationary.

Ever since the observation of Sinkler and Eshner (198), reports of the association of idiopathic, hypochromic anemia and pernicious anemia in the same family have appeared sporadically in the literature. Wintrobe and Beebe (253) and Miller and Dameshek (151) have collected these reports and considered at some length the relationship between the two anemias. Emphasizing the almost constant finding of achlorhydria in idiopathic, hypochromic anemia, Wintrobe and Beebe (253) wrote: "In this anemia, as in pernicious anemia, the fundamental disturbance is defective gastric secretion. As a consequence, there is faulty utilization or synthesis from the diet of material which is necessary for hemoglobin formation." Lundholm (137) expresses a similar view.

Thus, from the work of many investigators the hypothesis has gradually emerged that the problem of the mode of inheritance of pernicious anemia is essentially the problem of the inheritance of a defective gastric and possibly duodenal mucosa. The appearance of such mucosa in kindreds is probably to a large extent under the control of one or more dominant genes. Individuals with the inherited defect are most readily detected by achlorhydria or achylia. It is not clear whether some or all of the individuals with achlorhydria pass through a stage characterized by hypochlorhydria, nor whether a certain fraction of persons with the inherited defect remains permanently in the stage of hypochlorhydria. Of the individuals with the defective mucosa and achlorhydria, some develop pernicious anemia, others essential hypochromic anemia. Some, probably a majority, remain asymptomatic. The special susceptibility of the patient with pernicious anemia to gastric carcinoma has long been recognized (58); it seems probable that the common denominator here is again the defective gastric mucosa. The foregoing viewpoint, adumbrated in the writings of the British school (101), has perhaps most clearly been expressed by Weitz (1938,

quoted from 111). The detectable carriers of the disease are those individuals with achlorhydria, although of course it is not to be assumed that all individuals with achlorhydria are carriers. Askey (11) in particular has emphasized the importance of following these carriers closely.

A differential diagnosis is at present not clear-cut, but includes chronic gastritis, gastric carcinoma, gastric neurosis, oral sepsis, general debility, and severe anemia (232, 22, 25).

Clinicians over a period of many years have come to recognize a "pernicious anemia type," characterized by blond or prematurely gray hair, light colored eyes, a wide face, and broad chest with wide costal angles (cf. esp. 57). While this type is a statistical concept that cannot be relied upon in the diagnosis of individual cases, its existence suggests that the same inherited factor(s) responsible for the achlorhydria influences other bodily characteristics. For the time being, however, the best index to the presence of these genetic factors is the achlorhydria.

5. *Afibrinogenemia* is a very rare disease characterized by the absence of blood fibrinogen, with incoagulability of the blood and a consequent tendency to fatal hemorrhage. Primary fibrinogenopenia is a similar but less extreme condition, characterized by a marked decrease in fibrinogen. The frequency of the latter disease is unknown, since even in the face of a markedly reduced fibrinogen the coagulation of the blood tends to remain normal, and only the most extreme reductions are detected clinically. It is not clear whether the two conditions are separate entities, or whether in some instances at least they represent different phases in the life history of a single disease. Quick (181) has summarized the literature.

Risak (186), in reporting four cases of primary fibrinogenopenia, had definite evidence of a reduced fibrinogen in the mother of one case, and presumptive evidence of a low fibrinogen in the mother of two other cases. Wolf's (255) patient with fibrinogenopenia had lost three siblings because of hemorrhage. Macfarlane (141) reported the case of a boy with afibrinogenemia whose father had a fibrinogenopenia, and suggested a recessive inheritance for afibrinogenemia. Finally, Schönholzer (192) described a sibship of three: one, the proband, had afibrinogenemia, with fatal hemorrhage; the second had a reduced fibrinogen (0.13 gms.%); and the third had bled to death from the umbilicus at age 17 days. In view of the apparent association in families between the two conditions, Schönholzer (192) suggested that the factor responsible for afibrinogenemia was an incomplete recessive, and that heterozygous carriers could sometimes be detected by fibrinogenopenia, which must, of course, be distinguished from that seen in hepatic insufficiency, cachectic conditions, and following severe hemorrhage (232).

6. *Sex-linked, hypochromic, microcytic anemia.* Under the title of "Hereditary (? sex-linked) anemia," Rundles and Falls (188) have recently described two kindreds in which a number of the male members were afflicted with a very severe hypochromic, microcytic type of anemia. A portion of one of these kindreds had been previously described by Cooley (44). The degree of the anemia was much more severe in one kindred than in the other. No females

developed the disease, but the female parents of affected males, as well as certain other females in the families, had splenomegaly and usually showed slight but probably significant erythrocyte abnormalities—increased percentages of spherocytes and of small, pale ovalocytes. The authors feel that the trait is probably due to a sex-linked gene. The difference between the expression of the disease in the two sexes, if this is the proper interpretation of the inheritance of the condition, would appear to depend on the fact that affected males are homozygous, i.e., carry the gene in question on their single X-chromosome, whereas affected females are heterozygous, i.e., carry the gene on only one of their two X-chromosomes. The possibility of an autosomal dominant gene whose expression is largely suppressed in females cannot be excluded. It is not clear whether two

TABLE 3

The occurrence of cardiovascular disease in the families of individuals with hypertension, and in the families of control, non-hypertensive individuals

INVESTIGATOR	HYPERTENSIVE PERSONS		NON-HYPERTENSIVES (CONTROLS)	
	No.	% with family history of cardiovascular disease	No.	% with family history of cardiovascular disease
Barach (13)	40	95.0	—	—
Weitz (244)*	82	76.8	267	30.3
O'Hare et al. (167)	300	68.0	436	37.0
Blanton (20)	350	46.7	—	—
Nuzum and Elliot (164)	500	30.8	250	29.6
Glomset (81)†	?	39.0	?	10.0
Palmer (170)	100‡	48.0	100	38.0
	100§	58.0		
Allan (5)‖	485	99.0	—	—
Hines (93)	267	86.6	492¶	17.2
			116**	84.2
Feldt and Wenstrand (66)	2188	32.8	2188	29.7

* Figures limited to parents of probands.
† Probands were school children of unspecified age.
‡ Unselected hypertensives.
§ Hypertensives selected because of the completeness of the information available.
‖ It is not clear from the paper whether these are selected data.
¶ Normal blood pressure, normo-reactors to cold-pressor test.
** Normal blood pressure, hyper-reactors to cold-pressor test.

different anemias are represented in the two families, but in any case the female carriers appear to show changes which while not pathognomonic should in conjunction with the family history be quite suggestive, after other possible causes of a similar blood picture, such as an asymptomatic hemolytic process, have been eliminated.

D. *Disorders of the cardiovascular system*

1. *Essential hypertension* is a disease of unknown etiology characterized by an elevation of the blood pressure above the commonly accepted limits of normal with, in time, the cardiovascular consequences of such an elevation. In addi-

tion to scattered reports of families showing a high incidence of hypertension, there have been a number of systematic attacks on the question of the contribution of hereditary factors to the etiology of the disease. One approach to the question consists in examining the family histories of control and hypertensive individuals. The results of ten typical investigations of this type are summarized in table 3. By the large, hypertensives more often give a family history of cardiovascular disease than do non-hypertensives, roughly 63% as opposed to 27%. Allan (5) from his investigation was led to the possibility of a dominant inheritance.

A more exact approach to the question than the compilation of family histories consists of a study of blood pressure levels in the parents, siblings, and children of unselected hypertensives and controls. Ayman (12) has carried out an extensive and widely quoted investigation of this type. His findings are summarized below:

CONDITION OF PARENTS	NUMBER OF CHILDREN AGED 14–39 STUDIED	PERCENTAGE WITH A BLOOD PRESSURE OF 140/80 OR GREATER
		per cent
1) Both parents normal	210	5.5
2) One or both parents with labile hypertension, or hypertension observed once but parents not seen for confirmation	268	17.1
3) One or both parents with definite hypertension		
a) one parent affected	225	28.4
b) both parents affected	87	37.9

Ayman also observed that among the siblings of the normotensive parents, 37.3% of 70 examined showed hypertension, whereas among the siblings of the hypertensive parents, 65.3% of 86 examined were hypertensive. Essentially similar results have been reported by Weitz (244). The bulk of the evidence favors the existence of significant hereditary factors in the development of the disease.

It is widespread clinical impression that those individuals who are subject to the development of hypertension have certain distinguishing physical characteristics (57) as well as mental and "nervous" characteristics, namely, signs of vasomotor weakness (167) and a tendency to be "high-strung," hyperactive, and sthenic (157, 12). In the period prior to the development of sustained hypertension they may also be subject to the development of emotional hypertension (94). A stumbling block in the way of exact studies in the inheritance of this disease has been the lack of reliable objective measures for identifying these individuals. The cold-pressor test of Hines and Brown (97, 98) appears to reprepresent a first approximation to the desired objective measures. It consists simply in measuring the response of an individual's blood pressure to a standard stimulus, the immersion of a hand in ice water for 30 seconds. Hines and Brown (97, 98) reported that although practically all individuals with a normal blood pressure show a transient rise, some individuals show a much more marked

elevation than others. Hypertensives also tend to show a marked elevation. Hines (97, 93, 95, 96) has maintained that these hyper-reactors represent a pre-hypertensive phase of the syndrome designated as essential hypertension. The evidence for the inherited nature of the response to the cold-pressor test, and the relation of this response to hypertension, falls into three categories (93):

1) The incidence of a family history of hypertension is the same in hyper-reactors as in manifest hypertensives, and in either case is almost five times as great as in normo-reactors (table 3).

2) Identical twins show very similar responses, whereas fraternal twins do not.

3) The tendency to be a hyper-reactor appears to be transmitted from generation to generation in a regular fashion, leading Hines to write that "inasmuch as I so far have not found any hyper-reactor who did not have one parent who had hypertension or was a hyper-reactor, it is probable that the trait is inherited as a dominant characteristic".

Dieckmann and Michel (53) and Briggs and Oerting (26) have confirmed these observations in part, finding that both pregnant and non-pregnant individuals with a family history of hypertension were more frequently hyper-reactors than persons without such a family history. On the other hand, Pickering and Kissen (176) were unable to show that hypertensives exhibited a greater reaction to the cold-pressor test than non-hypertensives, and Chesley and Chesley (34) and Feldt and Wenstrand (65) did not find an increased family history of hypertension among the hyper-reactors whom they studied. The reason for the wide discrepancy between the results of various observers is not immediately apparent. It can only be said now that it is probable that there is an inherited predisposition to the development of hypertension, which predisposition may possibly be detected at an early age by an exaggerated response to certain standard stimuli. The differential diagnosis is not clear. The development of other test situations offers wide possibilities.

2. *Hereditary hemorrhagic telangiectasia* is a disease characterized by the appearance of small, often spider-like hemangiomata in the skin, mucous membranes, gastro-intestinal tract, etc. The vessels composing these angiomata are abnormally thin walled and subject to rupture with consequent epistaxis and gastro-intestinal hemorrhage. The angiomata are usually rare until the age of 30–40, when they tend to become more numerous and more prominent. The disease is inherited as if due to a dominant factor, although occasionally a generation may appear to be skipped (181, 252, 14, 214). Since the condition is rare, the marriage of two affected (heterozygous) persons must be extremely uncommon. However, Snyder and Doan (204) have recorded such a marriage, from which resulted a child showing at birth one large telangiectatic area on the upper chest. About five days after birth the child began to develop numerous similar, smaller areas, which appeared at a rapid rate. Death occurred at 2½ months because of a profound anemia due to superficial and internal hemorrhages from telangiectatic areas. It is reasonable to assume that the child had inherited the factor in question from both parents, i.e., was the homozygote.

By definition, then, we must regard the heterozygote as the carrier of a potentially much more serious and fulminating condition.

There is evidence that some of the other rare, dominant factors known in man may, like that responsible for hereditary hemorrhagic telangiectasis, have very serious effects when homozygous, although when heterozygous they produce only a mild abnormality. Mohr and Wriedt (153) have studied an extensive kindred segregating for a minor type of dominant brachyphalangy; from a cousin marriage of two affected (heterozygous) persons there resulted a severely crippled individual, presumably the homozygote, who lacked fingers and toes and died at the age of one year. Munro (159) reports on a marriage of two persons with the dominant type of hereditary sebaceous cysts. There resulted ten children, of whom three died in infancy. The history on the three who died was unsatisfactory but they appear to have had convulsions, mental aberrations, and other abnormalities, and it is suggested that "a gene which, in heterozygous form, produces a minor abnormality might, in homozygous form, cause a gross disorder, fatal in childhood." Ovalocytosis of the erythrocytes is transmitted as if due to a single dominant gene (217). There have been several reports of unexplained anemia associated with the ovalocytosis (235, 100, 118, 148) and the situation may be similar to that in congenital hemolytic jaundice, except that a much smaller proportion of individuals with the trait develop anemia. Wyandt, Bancroft, and Winship (258) have described an extensive pedigree of this condition which included a marriage between two affected persons. Three offspring of this union were available for study—one of these was a daughter "with elliptic cells and, in addition, spherocytes and other evidences of hemolytic icterus, such as splenomegaly, markedly increased fragility of the red cells, high reticulocyte count, and jaundice." It is possible she represents the homozygote, although she may also have been a heterozygote showing unusually marked changes.

E. Diseases of the skin

1. *Xeroderma pigmentosum* is a rare condition with onset in infancy and childhood, probably related to an abnormal sensitivity to light and characterized in its early stages by hyperpigmentation of the skin resembling ordinary freckles, and photophobia. Later there appear whitish, atrophic spots, telangiectasis, and warty growths of various types. Malignant changes are prone to occur in the lesions. Death usually occurs at an early age. The condition was for some time thought to be due to an autosomal recessive gene (197, 37, 145), but Haldane (87) produced evidence for regarding it as due to an incompletely sex-linked recessive. Macklin (146) has pointed out that sex ratios are disturbed in sibships in which the disease is segregating, a fact which tends to complicate Haldane's argument.

Siemens and Kohn (197) were the first to emphasize the occurrence of excessive freckling in some of the near relatives of patients with the disease. After reviewing the literature and their own extensive series of cases, they concluded that heavy freckling in the parents and siblings of patients was probably a mani-

festation of heterozygosity and a means of detecting carriers. This freckling, unlike the ordinary variety, shows no particular correlation with light colored hair, or fair skin. Subsequent observations have confirmed this impression (37).

2. *Keratosis follicularis spinulosa cum ophiasi* is a disease known from a single large pedigree published by Siemens (196). There is a marked difference between affected males and females. Affected males have a marked keratosis follicularis with secondary loss of hair, degeneration of the cornea, searring and deformity of the pinna of the ears, and hypertrophy of the skin of the palms and soles. Affected females as a rule show only a mild keratosis follicularis. The disease appears to be sex-linked in its inheritance. As in the case of the sex-linked anemia previously described, the difference between the expression of the disease in the two sexes appears to depend on the fact that affected males are homozygous, i.e., carry the factor in question on their single X-chromosome, whereas affected females are heterozygous, i.e., carry the factor on only one of their two X-chromosomes. The midly affected females may therefor be regarded as the carriers of a disease which is much more serious for the males.

3. *Anhidrotic ectodermal dysplasia* is a condition characterized by the absence of sweat glands; fine, pale, scanty hair; marked dental aplasia, which may amount to complete adentia; characteristic deformities in such teeth as are present; chronic atrophic rhinitis; occasional absence of the lachrymal glands; and general maldevelopment. Hyperpyrexia because of absence of the sweat glands is common. There is often a family history of the disease (summaries in 240, 36, 52). Two different modes of inheritance have been described. The majority of the pedigrees show sex-linked, recessive inheritance, males only being affected. However, some pedigrees are unusual in that both sexes are affected, but the females as a rule to a much milder degree than the males. These latter pedigrees permit of two explanations. One is that the condition is due to an autosomal dominant, expressed differently in the two sexes (36). The other explanation, suggested by Roberts (187) and Levit (130), is that the disease is due to a sex-linked gene which, being heterozygous in affected females but homozygous in affected males, as in the case of keratosis follicularis spinulosa and the anemia described previously, is more strongly expressed in males.[5]

F. Miscellaneous

1. *The Laurence-Moon-Biedl syndrome* when it reaches full expression is characterized by obesity, hypogenitalism, mental retardation, polydactyly, and retinal pigmentation. The disease is rare, and between 23 and 39% of the cases are the issue of consanguinous matings. Although the disease is inherited as a

[5] Falls and Cotterman, in an unpublished investigation which I am kindly permitted to quote, have recently studied a kindred in which there occurs a recessive, sex-linked type of retinitis pigmentosa. Although only males show typical retinitis pigmentosa, those females in the family who transmit the disease to their sons regularly possess a tapetum-like retina. Here, then, is a possible fourth example of a "recessive", sex-linked gene which has detectable effects in the heterozygous female carriers. Other sex-linked conditions in which a somewhat smaller proportion of heterozygous females may s[illegible] partures from normal are hemophilia and color-blindness.

recessive trait, there is a considerable difference of opinion in the literature as to whether it is determined by one, two, or more recessive genes (summaries in 37, 219, 205). It seems well established that various minor abnormalities (obesity, mental defect, retinal pigmentation, or polydactyly) suggestive of various aspects of the syndrome occur with increased frequency in families which produce children showing the complete syndrome. The literature on this point is very adequately summarized in the above quoted reviews, and needs no repetition here. This fact led Sorsby, Avery, and Cockayne (205) to write: "The large number of ascendants and collaterals with obesity, abnormalities of the skeletal system, or some other incomplete expression of the syndrome, shows that it is not always completely recessive and that heterozygotes are sometimes recognizable".

2. *Allergy.* Broadly defined, an *allergic* individual is one who, by comparison with most persons, has acquired the property of reacting excessively to contact of various types with certain substances. Observations on the hereditary nature of the allergic constitution date back several centuries, and by now a very considerable literature on the subject has been accumulated and is reviewed in standard works on allergy (35, 183, 237, 233). There is rather general agreement on the importance of hereditary influences in the appearance of allergic manifestations (although see 184), and there is even evidence that particular types of allergy—e.g., asthma, hay fever—tend to occur in certain families (35). The similarity of the allergic responses of identical twins provides strong evidence for the existence of very specific constitutional factors controlling the exact type of allergy (43, 48, 245). On the other hand, the ability to become sensitized to a potential allergen will never become evident without exposure to that allergen; genetically determined sensitization patterns must depend for their realization on the type and frequency of exposure to various allergens.

How the differences between individuals with respect to their allergic susceptibilities are inherited is not generally agreed upon. Early investigators, writing before the concept of the incomplete penetrance or irregular dominance of some genes had become generally recognized, attempted to fit the observations into a simple, formal scheme, with Cooke and Vander Veer (43) and Spain and Cooke (206) suggesting the action of a single dominant factor, and Adkinson (2) a recessive factor. Later it was recognized that neither explanation was satisfactory, and the dependence of allergy on an irregularly expressed dominant gene, which might fail to find any expression during the life time of some carriers, was suggested (185, 27). This theory, of an irregularly expressed dominant, has been further refined by Wiener, Zieve, and Friese (247). Cooke and Vander Veer (43) and later Balyeat (12a) showed clearly that where there is both a paternal and maternal history of allergy, the allergic offspring tend to develop their symptoms much earlier (the great majority by the seventh or eight year) than when the allergic history is only on one side of the family, or where there is no allergic history. Wiener, Zieve, and Fries suggest that this is so because the early development of the allergic state depends on homozygosity for a certain gene which must be introduced bilineally, whereas the later development of

allergic symptoms depends on heterozygosity for that same factor. However, only a fraction of the heterozygotes, whom they estimate at one-fifth to one-sixth of the total number, ever develops symptoms. According to this theory, then, individuals who develop symptoms after the age of puberty may be regarded as the carriers of a gene which when homozygous results in the earlier onset and greater severity of symptoms.

III. DISCUSSION

The chief contribution to medical theory of the recognition of carrier states consists in a broadening of concepts of inherited disease. Thus, the familial nature of gout has been recognized for a long time, but its sporadic occurrence in families suggested a rather complicated genetic mechanism. The discovery that in "gouty families" the tendency to hyperuricemia is transmitted in a simple, regular fashion, but that only a minority of persons with hyperuricemia develop gout clinically, clarifies the issue, and suggests the value of further studies on hyperuricemic individuals, searching for significant differences between those who develop gout and those who do not. Moreover, the observed difference between the expression in the two sexes of the gene responsible for hyperuricemia contributes to an understanding of why gout is so much more frequent in males than in females. Like gout, epilepsy, although familial, is of sporadic occurrence, its incidence in families falling short of any simple genetic proportion. The discovery of a high frequency of abnormal brain waves in the relatives, and especially the parents, of epileptics suggests that the dividing line between the epileptic and the non-epileptic is less definite than formerly supposed, with trauma of various types in many cases being the differential. Diabetes mellitus and pernicious anemia present analogous situations. On the more immediately practical side, there is the possibility that through the early detection of some of these carriers and appropriate action—such as adequate dietary restrictions in the case of carriers of diabetes and xanthomatosis—useful years may be added to their lives.

From the standpoint of the present accuracy of identification of the carrier state, the diseases which have been considered fall into three loose groups. 1) For five of the diseases described—gout, xanthomatosis, thalassemia, sickle cell anemia, and congenital hemolytic jaundice—the diagnosis of a carrier state may be made with considerable assurance after appropriate steps have been taken to exclude other possible causes of a similar picture. A high proportion of the carriers of these diseases can be identified even in the absence of an adequate family history. Certain rare dominant diseases, of which hereditary hemorrhagic telangiectasia was presented as a type form, also fall into this group, as does the sex-linked type of retinitis pigmentosa described by Falls and Cotterman. 2) A second group of diseases is composed of epilepsy, diabetes, pernicious anemia, and essential hypertension. Although many details remain to be worked out, it seems that a smaller proportion of the genetic carriers show recognizable changes than in the first group, and that, moreover, the differential diagnosis between the carrier state and other possible causes of a similar picture is more

difficult. A positive family history thus becomes a statistical adjunct to the diagnosis of the carrier states included in this group. 3) Finally, we have the remaining diseases, all rare and of little clinical significance, where the findings which reveal the carrier state are of a low degree of specificity, and assume significance primarily in connection with the family history. The facts with regard to allergy and phenylpyruvic amentia are still so controversial that they cannot be assigned to any group.

Of the 22 diseases mentioned, 11 affect the blood or skin. This disproportionate representation of dermatology and hematology is probably not entirely due to chance, but reflects the ease with which blood and skin can be studied, and the accuracy of anatomical and histological observation possible. A corollary of this is that the recognition of the carriers of other traits involving less readily accessible systems calls for closer observation of persons genetically related to the patient.

Considered with respect to the hereditary mechanisms involved, the inherited diseases for which a carrier state may be recognized clinically fall into four broad categories. The classification of several of these diseases is tentative, and may have to be changed in the light of subsequent findings.

1) Diseases dependent on one or more nominally recessive genes, which are completely penetrant when homzygous but also show slight effects when heterozygous, i.e., diseases dependent on semidominant or incompletely recessive genes. The clinically detectable carrier is a heterozygous individual showing minor but significant departures from the norm. This category includes not only conditions due to autosomal genes but also those caused by certain incompletely recessive, sex-linked genes. Conditions which appear to fall into this group on the basis of present information are thalassemia, hereditary hemorrhagic telangiectasia, ovalocytosis, brachyphalangy, one type of sebaceous cysts, Laurence-Moon-Biedl syndrome, phenylpyruvic amentia, keratosis follicularis spinulosa, a sex-linked type of hypochromic, microcytic anemia, a type of retinitis pigmentosa, xeroderma pigmentosa, ? afibrinogenemia, ? sickle cell anemia, ? anhidrotic ectodermal dysplasia, ? allergy. In some of these diseases, the heterozygote may be detected with a high degree of accuracy (thalassemia); in others, only occasionally (Laurence-Moon-Biedl syndrome).

2) Diseases dependent on an incompletely penetrant, recessive factor, in which the recognizable carrier is a homozygote who has the same genetic constitution with respect to the gene in question as does the individual with the disease, but who for reasons not understood, shows only minor aberrations. The sole disease considered which may fall into this group, in some pedigrees, is diabetes mellitus.

3) Diseases dependent on heterozygosity for an irregularly expressed, dominant gene or genes. The effects of these genes when homozygous have thus far not been described. The carrier is a heterozygote (just like the individual with the disease) in whom for some reason the gene fails to find the commonly recognized clinical expression, although its effects may still be detected. Diseases in this category include gout, primary essential xanthomatosis, congenital hemolytic jaundice, diabetes (some pedigrees), and ? sickle cell anemia.

4) Diseases in whose development hereditary influences are definitely involved but whose exact genetic basis remains obscure. The carriers are those individuals transmitting the disease who show significant detectable departures from the norm, without those achieving at the time clinical importance. For the present, allergy, pernicious anemia, and hypertension must be placed here, although it is possible that the former belongs in category 1, and the two latter in category 3.

There are several other possible categories of carriers, which with further refinement of the subject must be defined. However, the above enumerated are adequate for the present. In categories 2, 3, and 4 the distinction may be drawn between carriers who will never develop the full-blown disease and those who will later, often when their reproductive life is well under way or completed, show typical symptoms and signs.

The ratio of carriers to diseased varies with the frequency of the disease and the manner in which it is inherited. Let us consider for the moment a disease due to homozygosity for a recessive gene, a, whose normal allelomorph is A. Individuals whose genetic constitution is aa would have the disease, while those who were Aa would be carriers. The Hardy-Weinberg law (89, 242) states that in a population breeding at random and in equilibrium, the genotypes AA, Aa, and aa occur in the ratios $p^2:2pq:q^2$, where p is the frequency of A and q the frequency of a ($= 1-p$), and p plus $q = 1$. It is apparent that the number of persons in the population with the disease equals the number of carriers ($2pq = q^2$) when $q = 2/3$, i.e., when the frequency of $aa = 4/9$. At any frequency of the disease below 4/9, carriers are more frequent than diseased. Thus, when $aa = 0.01$, $Aa = 0.18$. If a disease is due to an irregularly expressed dominant gene, the ratio of carriers: diseased depends on the penetrance of the gene. In case the penetrance is below 50%, the number of carriers of course exceeds the number with the disease. In general, for most of the diseases discussed in this review, the number of carriers is much greater than the number with the disease. This statement also holds true for the many other diseases in which heredity plays a part, for which we are as yet unable to recognize a carrier state on clinical grounds. Considering the total number of diseases in which heredity is an important factor, it is not unlikely that on the average every individual is a carrier for at least one clear-cut, undesirable, pathological condition.

In the past, attempts have been made to explain some of the irregularly expressed inherited diseases in terms of two or more independently segregating genes. The recognition of carrier states suggests that some such explanations are incorrect, and that we have instead to consider the action of a "chief gene," whose exact expression is colored by the effects of minor modifiers and environmental factors.

Most of the diseases discussed have a relatively simple genetic basis. This simplicity leads to the possibility of genetic control. If all the carriers and persons afflicted with the diseases listed in group 3 above failed to reproduce, then, assuming complete ascertainment, these diseases would disappear in a single generation. The prevention of inter se marriages involving the different types of carriers listed in group 1 above would, again assuming complete

ascertainment, result in the disappearance of those diseases due to the homozygous condition (except for sex-linked traits) in a single generation. However, while we can recognize the possibility of genetic control of certain diseases, this is a possibility to be approached with great caution. Our knowledge of human heredity at this point is limited indeed. The consequences of introducing innovations in the treatment of the soma are by the large less far reaching than policies aimed at altering the genetic composition of a population which, once set into motion, have irreversible effects extending over all subsequent generations. One must be very certain of one's ground where eugenic measures are concerned. There will perhaps come a day when man will have sufficient knowledge to make desirable a comprehensive genetic program, as one aspect of a many faceted, self-directed program of human evolution. That day is not in the immediately foreseeable future.

LITERATURE CITED

1. Addison, T., and Gull, W.: On a certain affection of the skin, vitiligoidea—(a) plana; (b) tuberosa, with remarks. Guy's Hosp. Rep. **7**: 265, 1851.
2. Adkinson, J.: The behavior of bronchial asthma as an inherited character. Genetics **5**: 363, 1920
3. Alder, A.: Perniziöse Anëmie bei Zwillingen. Helv. Med. Acta **11**: 164, 1944.
4. Allan, W.: Heredity in diabetes. Ann. Int. Med. **6**: 1272, 1933.
5. Allan, W.: Heredity in hypertension. Arch. Int. Med. **52**: 954, 1933.
6. Allen, F. M., and Mitchell, J. W.: A case of hereditary diabetes. Arch. Int. Med. **25**: 648, 1920.
7. Anderson, H. B.: Sickle cell anemia. Report of an active case. Am. J. Med. Sci. **171**: 641, 1926.
8. Anderson, W., and Ware, R. L.: Sickle cell anemia. Am. J. Dis. Child. **44**: 1055, 1932.
9. Archibald, R. G.: A case of sickle cell anemia in the Sudan. Tr. Roy. Soc. Trop. Med. and Hyg. **19**: 389, 1926.
10. Arena, J. M.: Vascular accident and hemiplegia in a patient with sickle cell anemia. Am. J. Dis. Child. **49**: 722, 1935.
11. Askey, J. M.: Prevention of pernicious anemia: recognition of the latent stage in relatives. Ann. Int. Med. **14**: 593, 1940.
12. Ayman, D.: Heredity in arteriolar (essential) hypertension—a clinical study of the blood pressure of 1524 members of 277 families. Arch. Int. Med. **53**: 792, 1934.

12a Balyeat, R. M.: The hereditary factor in allergic diseases. Am. J. Med. Sci. **176**: 332, 1928.

13. Barach, J. H.: Essential vascular hypertension. J. A. M. A. **79**: 2140, 1922.
14. Barrock, J. J.: Hereditary hemorrhagic telangiectasia: report of case with review of the literature. Wisconsin Med. J. **43**: 805, 1944.
15. Baur, E., Fischer, E., and Lenz, F.: Human heredity. Third edition, translated by E. and C. Paul. New York: MacMillan Co. pp. 734. 1931.
16. Bauer, W., and Klemperer, F.: Gout. In Duncan, G. G.: Diseases of metabolism. Philadelphia: W. B. Saunders Co. pp. 609–654. 1942.
17. Bell, A. J., Kotte, R. H., Mitchell, A. G., Cooley, T. B., and Lee, P.: Sickle cell anemia. Report of two cases in young children in which splenectomy was performed. Am. J. Dis. Child. **34**: 923, 1927.
18. Berger, H.: Über das Elektrenkephalogramm des Menschen. Arch. f. Psych. **100**: 301, 1933.
19. Berk, L., and Bull, G. M.: A case of sickle cell anemia in an Indian woman. Clin. Proc. (J. Cape Town Post-Grad. Med. Ass.) **2**: 147, 1943.

20. Blanton, W. B.: A study in vascular hypertension. South. Med. and Surg. 92: 495, 1930.
21. Bloom, D., Kaufman, S. R., and Stevens, R. A.: Hereditary xanthomatosis. Arch. Dermat. and Syph. 45: 1, 1942.
22. Boeansky, M., and Boeansky, O.: Biochemistry of disease. New York: The MacMillan Co. pp. ix and 684. 1940.
23. Brain, W. R.: The inheritance of epilepsy. Quart. J. Med. 19: 299, 1926.
24. Brain, W. R.: Inheritance of epilepsy. In Blacker, C. P., The chances of morbid inheritance. Baltimore: Wm. Wood and Co. pp. 73-85. 1934.
25. Bray, W. E.: Synopsis of clinical laboratory methods. St. Louis: C. V. Mosby Co. pp. 528. 1941.
26. Briggs, J. F., and Gentino, H.: The prognostic value of the cold test in pregnancy. Minn. Med. 20: 382, 1937.
27. Bucher, C. S., and Keeler, C. E.: The inheritance of allergy. J. Allergy 5: 611, 1934.
28. Byers, R. K.: Electroencephalography. J. Pediat. 18: 811, 1941.
29. Caminopetros, J.: Recherches sur l'anémie erythroblastique infantile, des peuples de la Méditerranée orientale. Ann. de Méd. 43: 27, 101, 1938.
30. Cammidge, P. J.: Diabetes mellitus and heredity. Brit. Med. J. 2: 738, 1928.
31. Campbell, J. M. H., and Warner, E. C.: Heredity in acholuric jaundice. Quart. J. Med. 19: 333, 1926.
32. Canby, C. B., Carpenter, G., and Ellmore, L. F.: Drepanocytosis (sicklemia) and an apparently acute surgical condition of the abdomen. Arch. Surg. 48: 123, 1944.
33. Castle, W. B.: The etiology of pernicious anemia and related macrocytic anemias. Ann. Int. Med. 7: 2, 1933.
34. Chesley, L. C., and Chesley, E. R.: The cold pressor test in pregnancy. Surg., Gyn., and Ob. 69: 436, 1939.
35. Coca, A. F., Walzer, M., and Thommen, A. A.: Asthma and hay fever in theory and practice. Springfield: Charles C. Thomas. pp. vii and 851. 1931.
36. Cockayne, E. A.: Inherited abnormalities of the skin and its appendages. London: Oxford University Press. pp. x and 391. 1933.
37. Cockayne, E. A., Krestin, D., and Sorsby, A.: Obesity, hypogenitalism, mental retardation, polydactyly, and retinal pigmentation. The Laurence-Moon-Biedl syndrome. Quart. J. Med. N. S. 4: 93, 1935.
38. Cahn, A., and von Mering, J.: Die Säuren des gesunden und kranken Magens. Deutsches Arch. f. Klin. Med. 39: 233, 1886.
39. Cohen, A.: Gout. Am. J. Med. Sci. 192: 488, 1936.
40. Conner, H. M.: Hereditary aspect of achlorhydria in pernicious anemia. J. A. M. A. 94: 606, 1930.
41. Cook, J. E., and Meyer, J.: Severe anemia with remarkable elongated and sickle-shaped red blood cells and chronic leg ulcer. Arch. Int. Med. 16: 644, 1915.
42. Cooke, J. V., and Mack, J. K.: Sickle-cell anemia in a white American family. J. Pediat. 5: 601, 1934.
43. Cooke, R. A., and Vander Veer, A.: Human sensitization. J. Immunol. 1: 201, 1916.
44. Cooley, T. B.: A severe type of hereditary anemia with elliptocytosis. Am. J. Med. Sci. 209: 561, 1945.
45. Cooley, T. B., and Lee, P.: Series of cases of splenomegaly in children with anemia and peculiar bone changes. Tr. Am. Ped. Soc. 37: 29, 1925.
46. Cooley, T. B., and Lee, P.: The sickle cell phenomenon. Am. J. Dis. Child. 32: 334, 1926.
47. Cooley, T. B., and Lee, P.: Sickle cell anemia in a Greek family. Am. J. Dis. Child. 38: 103, 1929.
48. Chief, L. H.: Allergy in identical twins: report of seven pairs of twins. J. Allergy 13: 591, 1942.

49. Dacie, J. V.: Familial haemolytic anaemia (acholuric jaundice), with particular reference to changes in fragility produced by splenectomy. Quart. J. Med. **12**: 101, 1943.
50. Dameshek, W.: "Target cell" anemia: anerythroblastic type of Cooley's erythroblastic anemia. Am. J. Med. Sci. **200**: 445, 1940.
51. Dameshek, W.: Familial Mediterranean target-oval cell syndromes. Am. J. Med. Sci. **205**: 643, 1943.
51a. Davidson, L. S. P., and Gulland, G. L.: Pernicious anaemia. St. Louis: C. V. Mosby Co. pp. xii and 293. 1930.
52. de Silva, P. C. C.: Hereditary ectodermal dysplasia of anhydrotic type. Quart. J. Med. **8**: 97, 1939.
53. Dieckmann, W. J., and Michel, H. L.: Thermal study of vasomoter lability in pregnancy. Arch. Int. Med. **55**: 420, 1935.
54. Diggs, L. W.: The blood picture in sickle cell anemia. South. Med. J. **25**: 615, 1932.
55. Diggs, L. W., Ahmann, C. F., and Bibb, J.: The incidence and significance of the sickle cell trait. Ann. Int. Med. **7**: 769, 1933.
56. Dorst, S. E.: Familial pernicious anemia. A discussion of an unusual group of cases with a consideration of achlorhydria as the dominant etiologic factor. Am. J. Med. Sci. **172**: 173, 1926.
57. Draper, G., Dupertuis, C. W., and Caughey, J. L.: Human constitution in clinical medicine. New York: Paul B. Hoeber, Inc. pp. ix and 273. 1944.
58. Editorial: Gastric cancer and pernicious anemia. Lancet **2**: 406, 1945.
59. Editorial: Sickle cell trait and anemia. Lancet **2**: 204, 1946.
60. Emmel, V. E.: A study of the erythrocytes in a case of severe anemia with elongated and sickle-shaped red blood corpuscles. Arch. Int. Med. **20**: 586, 1917.
61. Engelberg. H., and Newman, B. A.: Xanthomatosis: a cause of coronary artery disease in young adults. J. A. M. A. **122**: 1167, 1943.
61a. Evans, R. W.: The sickling phenomenon in the blood of West African natives. Tr. Roy. Soc. Trop. Med. and Hyg. **37**: 281, 1944.
62. Fagge, C. H.: Two cases of vitiligoidea associated with chronic jaundice and enlargement of the liver. Tr. Path. Soc. London **19**: 434, 1868.
63. Falls, H. F., and Cotterman, C. W.: Unpublished data.
64. Fasold, A.: Studien über Vererbung von Hautkrankheiten. VI. Xanthom (Cholesterosis cutis). Arch. f. Rassen.—u. Gesellsch.-Biol. **16**: 54, 1924.
65. Feldt, R. H., and Wenstrand, D. E. W.: The cold pressor test in subjects with normal blood pressure: report on observations in 350 subjects, with special reference to the family history. Am. Heart J. **23**: 766, 1942.
66. Feldt, R. H., and Wenstrand, D. E. W.: The family history in arterial hypertension; study of 4376 insurance examinations. Am. J. Med. Sci. **205**: 61, 1943.
66a. Fenwick, S.: Atrophy of the stomach. Lancet **2**: 1, 1877.
67. Flaum, E., and Schlesinger, A.: Über eine Störung der Blutzuckerregulation bei familiärer diabetischer Belastung. Wiener Arch. f. Inn. Med. **22**: 131, 1932.
68. Folin, O., and Dennis, W.: The diagnostic value of uric acid determinations in blood. Arch. Int. Med. **16**: 33, 1915.
68. Föllings, A.: Über Ausscheidung von Phenylbrenztraubensäure in den Harn als Stoffwechselanomalie in Verbindung mit Imbezillität. Zeitschr. f. Physiol. Chem. **227**: 169, 1934.
70. Futcher, T. B.: The occurrence of gout in the United States; with an analysis of 36 cases. J. A. M. A. **39**: 1046, 1902.
71. Gaál, A. M.: Untersuchungen über Cholesterinstoffwechsel bei Xanthomatosis essentialis. Zeitschr. f. Klin. Med. **113**: 349, 1930.
72. Gänsslen, M.: Über hämolytischen Icterus. Deutsches Arch. f. Klin. Med. **140**: 210, 1922.
73. Garrod, A. B.: A treatise on gout and rheumatic gout (rheumatoid arthritis). Third edition. London: Longmans, Green, and Co. pp. xvi and 584. 1876.

74. Garrod, A. E.: The inborn factors in disease. New York: Oxford Press. pp. 160. 1931.
75. Gates, R. R.: Heredity in man. New York: MacMillan Co. pp. xii and 385. 1929.
75a. Gates R. R.: Human Genetics. New York: MacMillan Co. Vols. I and II. 1946.
76. Gibbs, F. A.: Electrical activity of the brain. Ann. Rev. Physiol. 7: 427, 1945.
77. Gibbs, F. A., Davis, H., and Lennox, W. G.: The electroencephalogram in epilepsy and in conditions of impaired consciousness. Arch. Neurol. and Psych. 34: 1133, 1935.
78. Gibbs, F. A., and Lennox, W. G.: Electroencephalography and epilepsy. Am. J. Psychiat. 100: 544, 1944.
79. Giffin, H. Z.: Hemolytic jaundice: a review of seventeen cases. Surg., Gyn., and Ob. 25: 152, 1917.
80. Gilman, R.: Electroencephalography: review of 1942. Psych. Bull. 41: 416, 1944.
81. Glomset, D. J.: Hereditary hypertension. J. Iowa State Med. Soc. 21: 220, 1931.
82. Gossage, A. M.: The inheritance of certain human abnormalities. Quart. J. Med. 1: 331, 1908.
83. Graham, G. S.: A case of sickle cell anemia with necropsy. Arch. Int. Med. 34: 778, 1924.
84. Graham, G. S., and McCarty, S. H.: Sickle cell (meniscocytic) anemia. South. Med. J. 23: 598, 1930.
85. Greisheimer, E. M., and Goldsworthy, E.: Glucose tolerance. Proc. Soc. Exp. Biol. and Med. 31: 1056, 1934.
86. Hahn, E. V., and Gillespie, E.: Sickle cell anemia. Report of a case greatly improved by splenectomy. Experimental study of sickle cell formation. Arch. Int. Med. 39: 233, 1927.
87. Haldane, J. B. S.: A search for incomplete sex-linkage in man. Ann. Eug. 7: 28, 1936.
88. Hansen, S.: Ueber die Vererbung des Diabetes mellitus. Acta Med. Scand. 62: 85, 1925.
89. Hardy, G. H.: Mendelian proportions in a mixed population. Science 28: 49, 1908.
90. Hayem, G.: Sur une variété particulière d'ictère chronique. Presse Méd., p. 121, 1898.
91. Herrmann, F., and Nathan, E.: Zur Frage der Xanthomgenese. Arch. f. Dermat. u. Syph. 152: 575, 1926.
92. Hill, L. C.: Gout. Lancet 1: 826, 1938.
93. Hines, E. A., Jr.: The hereditary factor in essential hypertension. Ann. Int. Med. 11: 593, 1937.
94. Hines, E. A., Jr.: Range of normal blood pressure and subsequent development of hypertension. J. A. M. A. 115: 271, 1940a.
95. Hines, E. A., Jr.: The significance of hyperreaction of the usually normal blood pressure. Med. Clin. N. Am. 24: 1089, 1940b.
96. Hines, E. A., Jr.: The significance of vascular hyperreaction as measured by the cold-pressor test. Am. Heart J. 19: 408, 1940c.
97. Hines, E. A., Jr., and Brown, G. E.: Standard stimulus for measuring vasomotor reactions: its application in the study of hypertension. Proc. Staff Meet. Mayo Clin. 7: 332, 1932.
98. Hines, E. A., Jr., and Brown, G. E.: The hereditary factor in the reaction of the blood pressure to a standard stimulus (cold). Preliminary report. Proc. Staff Meet. Mayo Clin. 10: 371, 1935.
99. Huck, J. G.: Sickle cell anaemia. Bull. Johns Hopkins Hosp. 34: 335, 1923.
100. Hunter, W. C., and Adams, R. B.: Hemotologic study of three generations of a white family showing elliptical erythrocytes. Ann. Int. Med. 2: 1162, 1929.
101. Hurst, A. F.: The pathogenesis of subacute combined degeneration of the spinal cord with special reference to its connection with Addison's (pernicious) anaemia, achlorhydria, and intestinal infection. Brain 48: 218, 1925.

102. Hutchinson, J.: On the hereditary transmission of gout. Med. Times and Gaz. **1:** 543, 1876.
103. Jacobson, B. M.: The uric acid in the serum of gouty and non-gouty individuals: its determination by Folin's recent method and its significance in the diagnosis of gout. Ann. Int. Med. **11:** 1277, 1938.
104. Jervis, G. A.: The genetics of phenylpyruvic oligophrenia. J. Ment. Sci. **85:** 719, 1939.
105. John, H. J.: A summary of the findings in 1,100 glucose tolerance estimations. Endocrin. **13:** 388, 1929.
106. Johnson, F. B., and Townsend, E. W.: Sickle cell anemia: a report of 30 cases. South. Med. and Surg. **99:** 377, 1937.
107. Jonas, C.: Dextrosebelastungskurven bei Verwandten von Diabetikern. Med. Klin. **33:** 802, 1937.
108. Joslin, E. P.: The treatment of diabetes mellitus. Philadelphia: Lea and Febiger. pp. 620. 1935.
109. Joslin, E. P., Dublin, L. I., and Marks, H. H.: Studies in diabetes mellitus. V. Heredity. Am. J. Med. Sci. **193:** 8, 1937.
110. Jung, F. A. R.: Die Haufigkeit und Erblichkeit von Magen-Darmbefunden in Familien. Arch f. Verdauungskr. **8:** 86, 1902.
111. Kaufmann, O., and Thiessen, K.: Zur Erbbiologie der perniziösen Anämie. Ztschr. f. Klin. Med. **136:** 474, 1939.
112. Kiefer, C. S., and Bloomfield, A. L.: The significance of gastric anacidity. Bull. Johns Hopkins Hosp. **39:** 304, 1926.
113. King, J. T., Jr., and Janeway, C. A.: Sickle cell anemia with cardiac complications. Internat. Clin., series 47, vol. **3:** 41, 1937.
114. Klatskin, G.: Familial xanthomatosis and arcus senilis. New Internat. Clin. **3:** 13, 1941.
115. Knode, K. T., and Giordano, A. S.: Sickle cell anemia. J. Indiana State Med. Ass. **33:** 78, 1940.
116. Lane, G. C., and Goodman, J., Jr.: Xanthoma tuberosum. Report of familial occurrence with probable cardiac lesions. Arch. Dermat. and Syph. **32:** 377, 1935.
117. Lapowski, B.: Familial xanthoma tuberosum multiplex in two sisters. Arch. Dermat. and Syph. **11:** 701, 1925.
118. Lawrence, J. S.: Human elliptical erythrocytes. Am. J. Med. Sci. **181:** 240, 1931.
119. Lawrence, R. D.: Heredity in diabetes mellitus and renal glycosuria. In Blacker, C. P., Chances of Morbid inheritance. Baltimore: Wm. Wood and Co. pp. 332–348. 1934.
120. Lemser, H.: Inwiewiet lässt sich eine nicht namifestierte Erbanlage für Diabetes mit Hilfe von Belastungsproben erkennen? Münchener Med. Wchschr. **85:**1657, 1938.
121. Lennox, W. G.: Mental defect in epilepsy and the influence of heredity. Am. J. Psychiat. **98:** 733, 1942.
122. Lennox, W. G.: Electrophysiology and epilepsy. Am. J. Psychiat. **98:** 592, 1942.
123. Lennox, W. G.: Electroencephalography and epilepsy. Am. J. Psychiat. **99:** 604, 1943.
124. Lennox, W. G.: Marriage and children for epileptics. Human Fert. **10:** 97, 1945.
125. Lennox, W. G., Gibbs, E. L., and Gibbs, F. A.: The inheritance of epilepsy as revealed by the electroencephalogram. J. A. M. A. **113:** 1002, 1939.
126. Lennox, W. G., Gibbs, E. L., and Gibbs, F. A.: Inheritance of cerebral dysrrhythmia and epilepsy. Arch. Neurol. and Psychiat. **44:** 1155, 1940.
127. Lennox, W. G., Gibbs, E. L., and Gibbs, F. A.: Twins, brain waves, and epilepsy. Arch. Neurol. and Psychiat. **47:** 702, 1942.
128. Lennox, W. G., and Gibbs, E. L.: The intelligence and the electroencephalograms of normal and epileptic twins. Tr. Am. Neurol. Ass. **70:** 182, 1944.
129. Lerman, J., Pierce, F. D., and Brogan, A. J.: Gastric acidity in normal individuals. J. Clin. Invest. **11:** 155, 1932.

130. Levit, S. G.: The problem of dominance in man. J. Genetics 33: 411, 1936.
131. Levit, S. G., and Pessikova, L. N.: The genetics of diabetes mellitus. Proc. Maxim. Gorky Med.-Biol. Res. Inst. 3:132, 1934 (Russian).
132. Lewis, J. H.: The biology of the negro. Chicago: University of Chicago Press. pp. xvii and 433, 1942.
133. Licht, J. A.: The early or premonitory symptoms of pernicious anemia. J. A. M. A. 48: 2177, 1907.
134. Lindsay, J.: Gout; its aetiology, pathology, and treatment. London: Henry Frowde, Hodder, and Stoughton. pp. 212. 1913.
135. Lowenbach, H.: The electroencephalogram in healthy relatives of epileptics. Bull. Johns Hopkins Hosp. 65: 125, 1939.
136. Luff, A. P.: Gout; its pathology, forms, diagnosis, and treatment. New York: Wm. Wood and Co. Third edition. pp. 290. 1907.
137. Lunnholm, I.: Über den Erbgang bei Anaemia hypochromica essentialis (achylia et non achylia). Acta Med. Scand., Suppl. 89: 157, 1938.
138. McCracken, J. P., Owen, P. S., and Pratt, J. H.: Gout: still a forgotten disease. J. A. M. A. 131: 367, 1946.
139. McGavack, T. H., and German, W. M.: Sicklemia in the Black Carib Indian. Am. J. Med. Sci. 208: 350, 1944.
140. McIntosh, R., and Woon, C. L.: An inquiry into the genetic factor in Cooley's anemia. Am. J. Dis. Child. 64: 192, 1942.
141. MacFarlane, R. G.: A boy with no fibrinogen. Lancet 1: 309, 1938.
142. Macheno, O., and Arosteoui de la O.: A case of sickle cell anemia. Arch. de Med. Inf. 10: 91, 1941.
143. Mackler, H. S., and Fischer, A. E.: The sugar tolerance in siblings of juvenile diabetic patients. J. A. M. A. 103: 240, 1934.
144. Macklin, M. T.: Inherited anomalies of metabolism. I. Diabetes mellitus. J. Hered. 24: 349, 1933.
145. Macklin, M. T.: Xeroderma pigmentosum. Arch. Dermat. and Syph. 34: 656, 1936.
146. Macklin, M. T.: Xeroderma pigmentosum. Arch. Dermat. and Syph. 49: 157, 1944.
147. Martius, F.: Achylia gastrica und perniziöse Anamie. Med. Klin. 12: 481, 1916.
148. Mason, V. R.: Ovalocytosis. In Downey, H.: Handbook of hematology. New York: Paul B. Hoeber, Inc. Vol. 3, pp. 2351–2360. 1938.
149. Meulengracht, E.: Über die Erblichkeitsverhältnisse beim chronischen hereditaren hämolytischen Ikterus. Deutsches Arch. f. Klin. Med. 136: 33, 1921.
150. Meulengracht, E.: The hereditary factor in pernicious anemia. Am. J. Med. Sci. 169: 177, 1925.
151. Miller, E. B., and Dameshek, W.: "Primary" hypochromic anemia terminating in pernicious anemia. Arch. Int. Med. 68: 375, 1941.
152. Minkowski, O.: Ueber eine hereditäre, unter dem Bilde eines chronischen Ieterus mit Urobilinurie, Splenomegalie und Nierensiderosis verlaufende Affection. Verhandl. d. Congr. f. Inn. Med., Wiesbaden, 18: 316, 1900.
153. Mohr, O. L., and Wriedt, C.: A new type of hereditary brachyphalangy in man. Car. Inst. Wash. Publ. 295, pp. 64. 1919.
154. Monchieff, A., and Whitby, L. E. H.: Cooley's anemia. Lancet 2: 648, 1934.
155. Monroe, R. T.: The detection of gout. Med. Clin. N. Am. 18: 999, 1935.
156. Morrison, M., Samwick, A. A., and Lansberg, E.: Sickle cell anemia in the white race: report of two cases with diagnosis by splenic puncture. Am. J. Dis. Child. 64: 881, 1942.
157. Moschcowitz, E.: Cause of hypertension of the greater circulation. J. A. M. A. 93: 347, 1929.
158. Müller, C.: Angina pectoris in hereditary xanthomatosis. Arch. Int. Med. 64: 675, 1939.
159. Munro, T. A.: Hereditary sebaceous cysts. J. Genetics 35: 61, 1937.

160. NAEGELI, O.: Blutkrankheiten und Blutdiagnostik. Berlin: Julius Springer. pp. xvii and 704. 1932.
161. NEEL, J. V., AND VALENTINE, W. N.: The frequency of thalassemia. Am. J. Med. Sci. 209: 568, 1945.
162. NEEL, J. V., AND VALENTINE, W. N.: Further studies on the genetics of thalassemia. Genetics, in press.
163. NEUBERGER, J.: Ueber das familiäre und konstitutionelle Moment in der Aetiologie der Anaemia perniciosa. Deut. Med. Wchnschr. 51: 1557, 1925.
164. NUZUM, F. R., AND ELLIOT, A. H.: An analysis of 500 instances of arterial hypertension. Am. J. Med. Sci. 181: 630, 1931.
165. OGDEN, M. A.: Sickle cell anemia in the white race, with report of cases in two families. Arch. Int. Med. 71: 164, 1943.
166. O'HARE, J. P.: Glucose tolerance test in chronic vascular hypertension. Med. Rec. N. Y. 98: 164, 1920.
167. O'HARE, J. P., WALKER, W. G., AND VICKERS, M. C.: Heredity and hypertension. J. A. M. A. 83: 27, 1924.
168. ORTIZ, A.: Anemia meniscocitica (sickle cell anemia). Bol. Asoc. Med. Puerto Rica 32: 273, 1940.
169. PAGE, E. W., AND SILTON, M. Z.: Pregnancy complicated by sickle cell anemia. Am. J. Ob. and Gyn. 37: 53, 1939.
170. PALMER, R. S.: Etiologic factors in hypertension. N. E. J. Med. 205: 1233, 1931.
171. PANNHORST, R.: Die Bedeutung des conjugalen Diabetes für die Erblichkeitsfrage der Zuckerkrankheit. Verhandl. d. Deut. Gesellsch. f. Inn. Med. 48: 411, 1936.
172. PENFIELD, W., AND ERICKSON, T. E.: Epilepsy and cerebral localization. Springfield: Charles C. Thomas. pp. x and 623. 1941.
173. PENROSE, L. S.: Two cases of phenylpyruvic amentia. Lancet 1: 23, 1935.
174. PENROSE, L. S.: The inheritance of phenylpyruvic amentia (phenylketonuria). Lancet 2: 192, 1935.
175. PENROSE, L. S.: Phenylketonuria. Lancet 1: 949, 1946.
176. PICKERING, G. W., AND KISSIN, M.: The effects of adrenaline and of cold on the blood pressure in human hypertension. Clin. Sci. 2: 201, 1936.
177. PINCUS, G., AND WHITE, P.: On the inheritance of diabetes mellitus. I. An analysis of 675 family histories. Am. J. Med. Sci. 186: 1, 1933.
178. PINCUS, G., AND WHITE, P.: On the inheritance of diabetes mellitus. II. Further analysis of family histories. Am. J. Med. Sci. 188: 159, 1934.
179. PINCUS, G., AND WHITE, P.: On the inheritance of diabetes militus. III. The blood sugar values of the relatives of diabetics. Am. J. Med. Sci. 188: 782, 1934.
180. QUECKENSTEDT: Die perniziöse Anämie. Deut. Med. Wchnschr. 39: 883, 1913.
181. QUICK, A. J.: The hemorrhagic diseases and the physiology of hemostasis. Springfield: Charles C. Thomas. pp. xvii and 340. 1942.
182. RACE, R. R.: On the inheritance and linkage relationships of acholurie jaundice. Ann. Eug. 11: 365, 1942.
183. RACKEMANN, F. M.: Clinical allergy. New York: The MacMillan Co. pp. xx and 617. 1931.
184. RATNER, B.: Does heredity play a role in the pathogenesis of allergy? J. Allergy 8: 273, 1936.
185. RICHARDS, M. H., AND BALYEAT, R.: The inheritance of allergy with special reference to migraine. Genetics 18: 129, 1933.
186. RISAK, E.: Die Fibrinopenie. Ztschr. Klin. Med. 128: 605, 1935.
187. ROBERTS, E.: Inheritance of anhidrosis associated with anadontia. J. A. M. A. 93: 277, 1929.
188. RUNDLES, R. W., AND FALLS, H. F.: Hereditary (?sex-linked) anemia. Am. J. Med. Sci. 211: 641, 1946.
189. RUSSELL, H., AND TAYLOR, C. J. S. O.: A case of sickle cell anemia. West African Med. J. 5: 68, 1932.

190. Schmidt, E.: Beitrage zur Xanthomfrage. Arch. f. Dermat. u. Syph. 140: 408, 1922.
191. Schoenheimer, R.: Über eine Störung der Cholesterin-Ausscheidung. Ztschr. f. Klin. Med. 123: 749, 1933.
192. Schönholzer, G.: Die hereditäre Fibrinogenopenie. Deut. Arch. f. Klin. Med. 184: 490, 1939.
193. Scudamore, C.: A treatise on the nature and cure of gout and rheumatism, including general considerations on morbid states of the digestive organs; some remarks on regimen; and practical observations on gravel. London: Joseph Mallet. Third edition. pp. 734. 1819.
194. Seestedt, H.: Blutzuckerkurven bei Geschwistern zuckerkranker Kinder. Deutsches Arch. f. Klin. Med. 172: 228, 1931.
194a. Sherman, I. J.: The sickling phenomenon, with special reference to the differentiaton of sickle cell anemia from the sickle cell trait. Bull. Johns Hopkins Hosp. 67: 309, 1940.
195. Sherrill, J. W.: The diagnosis of latent or incipient diabetes. J. A. M. A. 77: 1779, 1921.
196. Siemens, H. W.: Ueber einen, in der menschlichen Pathologie noch nicht beobachteten Vererbungsmodus: dominant-geschlechtsgebunde Vererbung. Arch. f. Rassen.—u. Gesellschaftsbiol. 17: 47, 1925.
197. Siemens, H. W., and Kohn, E.: Studien über Vererbung von Hautkrankheiten. IX. Xerodorma pigmentosum. Zeitschr. f. Ind. Abst. u. Vererb. 38: 1, 1925.
198. Sinkler, W., and Eshner, A. A.: Three cases of essential anemia in one family—father and two daughters. Am. J. Med. Sci. 112: 287, 1896.
199. Sjogren, T.: Die juvenile amaurotische Idiotie. Klinische und erblichkeitsmedizinische Untersuchungen. Hereditas 14: 197, 1931.
200. Smith, C. H.: Mediterranean (Cooley's) anemia in a youth of nineteen years observed since early childhood. J. Pediat. 20: 370, 1942.
201. Smith, C. H.: Familial blood studies in cases of Mediterranean (Cooley's) anemia. Am. J. Dis. Child. 65: 681, 1943.
202. Smith, J. H., Jr.: Sickle cell anemia. Med. Clin. N. Am. 11: 1171, 1928.
203. Smyth, C. J., and Freyberg, R. H.: A study of the hereditary nature of gout; a report of two families. Ann. Int. Med. 16: 46, 1942.
204. Snyder, L. H., and Doan, C. A.: Studies in human inheritance. XXV. Is the homozygous form of multiple telangiectasia lethal? J. Lab. and Clin. Med. 29: 1211, 1944.
205. Sorsby, A., Avery, H., and Cockayne, E. A.: Obesity, hypogenitalism, mental retardation, polydactyly, and retinal pigmentation. The Laurence-Moon-Biedl syndrome. Quart. J. Med. N. S. 8: 51, 1939.
206. Spain, W. C., and Cooke, R. A.: Studies in specific hypersensitiveness. XI. The familial occurrence of hay fever and bronchial asthma. J. Immunol. 9: 521, 1924.
207. Sperry, W. M., and Schick, B.: Essential xanthomatosis: treatment with cholesterol free diet in two cases. Am. J. Dis. Child. 51: 1372, 1936.
208. Sponaro, A., and Forkner, C. E.: Benign familial polycythemia. Arch. Int. Med. 52: 593, 1933.
209. Stamos, H. F.: Heredity in pernicious anemia. Am. J. Med. Sci. 200: 586, 1940.
210. Stein, C.: Hereditary factors in epilepsy. Am. J. Psychiat. 12: 989, 1933.
211. Steinberg, B.: Sickle cell anemia. Arch. of Path. 9: 876, 1930.
212. Steiner, F.: Untersuchungen zur Frage der Erblichkeit des Diabetes mellitus. Deutsches Arch. f. Klin. Med. 178: 497, 1936.
213. Stewart, W. B.: Sickle cell anemia: report of a case with splenectomy. Am. J. Dis. Child. 34: 72, 1927.
214. Stock, M. F.: Hereditary hemorrhagic telangiectasia (Osler's disease): a review of the literature and report of cases. Arch. Otolaryngol. 40: 108, 1944.
215. Strandskov, H. H.: Physiological aspects of human genetics, five human blood characteristics. Physiol. Rev. 24: 445, 1944.

216. Strauss, H., Rahm, W. E., and Barrera, S. E.: Electroencephalographic studies in relatives of epileptics. Proc. Soc. Exp. Biol. and Med. **42**: 207, 1939.
217. Strauss, M. B., and Daland, G. A.: Hereditary ovalocytosis (human elliptical erythrocytes): observations on ten cases in one family. N. E. Med. **217**: 100, 1937.
218. Strauss, M. B., Daland, G. A., and Fox, H. J.: Familial microcytic anemia. Am. J. Med. Sci. **201**: 30, 1941.
219. Streiff, E. B., and Zeltner, C.: Le syndrome de Laurence-Moon-Biedl. Arch. d'Ophth. N. S. **2**: 289, 1938.
220. Svendsen, M.: Are supernormal cholesterol-values in serum caused by a dominantly inherited factor? Report of a family investigation of 34 individuals. Acta Med. Scand. **104**: 235, 1940.
221. Sydenstricker, V. P.: Sickle-cell anemia. South. Med. J. **17**: 177, 1924.
222. Sydenstricker, V. P.: Further observations on sickle-cell anemia. J. A. M. A. **83**: 12, 1924.
223. Sydenstricker, V. P.: Sickle-cell anemia. Med. Clin. N. Am. **12**: 1451, 1929.
224. Sydenstricker, V. P., Mulherin, W. A., and Houseal, R. W.: Sickle-cell anemia. Am. J. Dis. Child. **26**: 132, 1923.
225. Talbott, J. H.: Serum urate in relatives of gouty patients. J. Clin. Invest. **19**: 645, 1940.
225a. Taliaferro, W. H., and Huck, J. G.: The inheritance of sickle-cell anaemia in man. Genetics **8**: 594, 1923.
226. Thannhauser, S. J.: Lipidoses: diseases of the cellular lipid metabolism. London: Oxford University Press. pp. xvii and 370. 1940.
227. Thannhauser, S. J., and Magendantz, H.: The different clinical groups of xanthomatous diseases; a clinical physiological study of 22 cases. Ann. Int. Med. **11**: 1662, 1938.
228. Then Bergh, H.: Die Erbbiologie des Diabetes mellitus. Vorlaufiges Ergebnis der Zwillungsuntersuchungen. Arch. f. Rassen.—u. Gesellschaftsbiol. **32**: 289, 1938.
229. Tomlinson, W. J.: The incidence of sicklemia and sickle cell anemia in 3000 Canal Zone examinations upon natives of Central America. Am. J. Med. Sci. **209**: 181, 1945.
230. Török, L.: De la natur des xanthomes avec quelques remarques critiques sur la notion des tumeurs. Ann. de Dermat. et de Syph. **31**: 393, 1911.
231. Trowell, H. C.: Sickle cell anemia. E. African Med. J. **22**: 34, 1945.
232. Trumper, M., and Cantarow, A.: Biochemistry in internal medicine. Philadelphia: W. B. Saunders Co. pp. 454. 1932.
Cantarow, A., and Trumper, M.: Clinical biochemistry. Third edition. Philadelphia: W. B. Saunders Co. pp. xvi and 647. 1945.
233. Urbach, E., and Gottlieb, P.: Allergy. New York: Grune and Stratton. pp. xxi and 1073. 1943.
234. Valentine, W. N., and Neel, J. V.: Hematologic and genetic study of the transmission of thalassemia. Arch. Int. Med. **74**: 185, 1944.
235. van den Bergh, A. A. H.: Elliptische rote Blutkörperchen, Addendum. Deut. Med. Wchnschr. **54**: 1244, 1928.
236. Vanzant, F. R., Alvarez, W. C., Eusterman, G. B., Dunn, H. L., and Berkson, J.: The normal range of gastric acidity from youth to old age. Arch. Int. Med. **49**: 345, 1932.
237. Vaughan, W. T.: The practice of allergy. St. Louis: The C. V. Mosby Co. pp. xvi and 1082. 1939.
238. Wallace, S. A., and Killingsworth, W. P.: Sicklemia in the Mexican race. Am. J. Dis. Child. **50**: 1208, 1935.
239. Weber, P. F.: Cutaneous xanthoma and "xanthomatosis" of other parts of the body—Pituitary xanthomatosis—"Xanthomyelomata" of tendon sheaths, etc., and the "Cholesterin Diathesis". Brit. J. Dermat. **36**: 335, 1924.

240. Weech, A. A.: Hereditary ectodermal dysplasia (congenital ectodermal defect). Am. J. Dis. Child. 37: 766, 1929.
241. Weinberg, F.: Achylia gastrica und perniziöse Anamie. Deutsches Arch. f. Klin. Med. 126: 447, 1918.
242. Weinberg, W.: Über den Nachweis der Vererbung beim Menschen. Jahrsh. Verein f. vaterländc Naturk., Wurttemberg, 64: 368, 1908.
243. Weinen, S. B.: Sickle cell anemia in an Italian child. J. Mt. Sinai Hosp. 4: 88, 1937.
244. Weitz, W.: Zur Ätiologie der genuinen oder vasculären Hypertension. Ztschr. f. Klin. Med. 96: 151, 1923.
245. Wenne, J., and Gannow, I.: Fatal anaphylactic shock; occurrence in identical twins following second injection of diphtherin toxoid and pertussis antigen. J. A. M. A. 131: 730, 1946.
246. Wenner, M.: Über die Erblichkeit der perniziosen Anämie auf Grund von klinischen Untersuchungen in 57 Sippen. Verh. Deut. Ges. Inn. Med. 50: 303, 1938.
247. Wiener, A. S., Zieve, I., and Fries, J. H.: The inheritance of allergic disease. Ann. Eug. 7: 141, 1936.
248. Wilkinson, J. F., and Brockbank, W.: Importance of familial achlorhydria in aetiology of pernicious anemia. Quart J. Med. 24: 219, 1931.
249. Williamson, C. S.: Gout; a clinical study of one hundred and sixteen cases. J. A. M. A. 74: 1625, 1920.
250. Wilson, C.: Some cases showing hereditary enlargement of the spleen. Trans. Clin. Soc. London 23: 162, 1890.
251. Wilson, C., and Stanley, D.: A sequel to some cases showing hereditary enlargment of the spleen. Trans. Clin. Soc. London. 26: 163, 1893.
252. Wintrobe, M. M.: Clinical hematology. Philadelphia: Lea and Febiger. pp. 792. 1942.
253. Wintrobe, M. M., and Beebe, R. T.: Idiopathic hypochromic anemia. Med. 12: 187, 1933.
254. Wintrobe, M. M., Mathews, E., Pollack, R., and Donyns, B. M.: A familial hemopoietic disorder in Italian adolescents and adults. J. A. M. A. 114: 1530, 1940.
255. Wolf, J.: Verblutungstod wegen Fibrinmangels. Jb. Kinderheilk. 148: 33, 1936.
256. Wollstein, M., and Kreidel, K. V.: Sickle cell anemia. Am. J. Dis. Child. 36: 998, 1928.
257. Wright, I. S.: Hereditary and familial diabetes mellitus. Am. J. Med. Sci 182: 484, 1931.
258. Wyandt, H., Bancroft, P. M., and Winship, T. O.: Elliptic erythrocytes in man. Arch. Int. Med. 68: 1043, 1941.
259. Zadek, I.: Laboratoriumsbefunde bei perniziöser Anamie. Ztschr. f. Klin. Med. 103: 646, 1926.

SCIENTIFIC PRINCIPLES, METHODS, AND RESULTS OF CHEMOTHERAPY, 1946

E. K. MARSHALL, JR.

Department of Pharmacology and Experimental Therapeutics, The Johns Hopkins University

At the 17th International Congress of Medicine held in London in 1913, Ehrlich gave an address entitled "Chemotherapeutics, Scientific Principles, Methods and Results" (1). Now a third of a century later, it may be profitable to see what are the present scientific principles, methods and results of chemotherapy.[1]

Ehrlich introduced the term "Chemotherapy" in order to mark off from the general field of pharmacology a particular type of investigation having as its object the discovery of chemicals acting specifically on parasitic infections. He limited the term to the treatment of systemic infections with compounds of known chemical structure in order not to include the local use of antiseptics and anthelmintics or the systemic use of antitoxins, serums, and vaccines. The term has frequently been much broadened in its connotation. Thus, one finds articles on the chemotherapy of thyroid disease (2). On the other hand, in strict accord with Ehrlich's definition the penicillins could not be considered chemotherapeutic agents until their chemical structure had been demonstrated.

Some justification would appear to have existed in Ehrlich's time for marking off from the general field of pharmacology the subject of chemotherapy. Pharmacology had devoted attention to the detailed analysis of symptoms on the higher animals of such drugs as quinine, the main therapeutic effect of which was the "cure" of a malarial attack (3). In addition, experiments with quinine were all of the acute type, while for its therapeutic use one was much more interested in its subacute or chronic administration. On the other hand, Ehrlich was interested in the antiparasitic action of quinine and wished to know more about it, but obtained no help from the orthodox pharmacologists. However, it seems likely that as much attention must be paid to the host-drug relationship as to the parasite-drug relationship. We now realize that a careful study of the toxicity, absorption, excretion, fate and distribution of a chemotherapeutic agent is just as important for devising its best use in a human infection as is a study of its antiparasitic properties in suitable experimental infections. It appears probable that if the most rapid and certain therapeutic advance is to be made chemotherapy must be recognized as an essential and important part of the general field of pharmacology.

From the beginning of his efforts in chemotherapy, Ehrlich emphasized the importance of mechanism of action. Largely on the basis of his immunological

[1] Examples for this discussion have been taken almost entirely from fields of chemotherapy with which the author has obtained some familiarity by investigation of these fields. Obviously, many other important fields might be used to give examples. Apology for omission is made to workers in these other fields.

studies, he developed his well known side-chain theory of chemotherapeutic action. In this 1913 address he states "destructive toxins develop their injurious action on the cell by the fact that they are absorbed by certain specific component parts of the cell—side chains—which I have characterized as receptors." This idea was transferred to chemical substances and the receptors were designated as chemoreceptors.[2] These chemoreceptors or side chains were supposed to combine with certain groups of the chemical agent and even secondary groups of the same might combine with other receptors of the cell more firmly fixing the drug. Thus, his golden rule of chemotherapy was to find chemicals which are maximally "parasitotropic" and minimally "organotropic," or ideally to select for fixation a chemoreceptor on the parasite which does not occur on the body cells. In regard to this, Ehrlich writes: "I have explained above that the parasites possess a whole series of chemo-receptors which are specifically different from one another. Now, if we can succeed in discovering among them a grouping which has no analogue in the organs of the body, then we should have the possibility of constructing an ideal remedy if we select a haptophoric group which is especially adjusted to the functions of the parasites. A remedy provided with such a haptophoric group would be entirely innocuous in itself, as it is not fixed by the organs; it would, however, strike the parasites with full intensity, and in this sense it would correspond to the immune productions, to the anti-substances discovered by Behring, and which after the manner of bewitched balls, fly in search of the enemy."

Compare this idea expressed by Ehrlich with that expressed in 1946 by an enzyme chemist in his discussion of the rational program of chemotherapy (4). The latter writes: "From the standpoint of enzymes, chemotherapy would appear to be the science of compounds which go for the enzymic Achilles' heel of an infectious organism without at the same time damaging the host unduly. In other words, the objective is first to find an enzyme which is present or important in the infectious organism and not in the host, and second to find a drug which specifically inhibits this enzyme." If we substitute receptor for enzyme, we are listening to Ehrlich a third of a century ago, and to "go for the enzymic Achilles's heel of an infectious organism" is certainly reminiscent of Ehrlich's "magic bullet."

This side-chain theory has been subjected to not only a great deal of criticism, but also has been considered fanciful, nonsensical, and absurd in the thirty years or more since Ehrlich proposed it. However, if one makes even a minimal allowance for the great advances in the biochemistry of the cell since Ehrlich proposed his theory, one is certainly impressed with the fundamental soundness of his general concepts. In fact, have we today a better word than "receptor" to express a localized portion of a cell? If one regards the -SH group of either certain parasites or body cells as a receptor for arsenic and mercury compounds, one finds from the most modern work a basis for hypotheses differing little from Ehrlich's fundamental concept.

[2] The fact that Ehrlich supposed the receptors to combine with food material as well as poisons makes one wonder if he did not have in its simplest form the most modern idea of metabolite antagonists as a guiding principle of chemotherapy.

Although, as we have seen, Ehrlich insisted on a rational basis for an understanding of the chemotherapeutic process—the action of the drug on the parasite—, aside from observations on gross toxicity little attention was given to the effects of the drug on the host or to the processes of absorption, distribution, excretion and degradation which modern work has shown to be important in the investigation of a chemotherapeutic agent. After Ehrlich's conception of a *therapia sterilizans magna*, where one dose of drug would completely eradicate the infection, failed with arsphenamine in human syphilis, the dosage schedule of arsenic compounds was not based on a carefully controlled experimental study. In fact, nearly thirty years has elapsed before studies were undertaken with a view of constructing a rational dosage schedule for the arsenical treatment of syphilis (5). In like manner, it was not until about 10 years after its introduction into therapeutics that the pharmacological effects of the arsphenamines on the mammalian organism were seriously investigated. One might believe that these defects in the study of a chemotherapeutic agent were due partly to the fact that Ehrlich deliberately attempted to remove chemotherapy from the general field of pharmacology.

Until the advent of the extensive investigations of the sulfonamides in bacterial chemotherapy in 1937, advance was slow in the principles and methods of chemotherapy. However, results were impressive. A number of new and valuable chemotherapeutic agents against protozoan infections were discovered: to mention only a few, there were pamaquine and quinacrine for malaria, carbarsone and chiniofon for amoebiasis, and tryparsamide and germanin for trypanosomiasis. However, either accident or a pursuance of the classical Ehrlich method of experimentation led to these discoveries, and little of value was contributed to an understanding of the chemotherapeutic process. In fact, the rather naive philosophy of Ehrlich was discarded, and very complicated and totally unproven assumptions made to explain the chemotherapeutic process. Some mysterious effect of the drug was postulated on the defence mechanisms of the host. Workers (6) in 1917 on the effect of emetine in amoebic dysentery and in 1936 on the effect of prontosil on streptococcic infections (7) concluded that the effect of the drug could not be upon the parasite, but must be exerted in some curious way upon the host cells. Later, when more light was shed upon these matters, it was found that the chemotherapeutic effect could be explained by a primary effect of the drug upon the parasite (8, 9). It is now generally accepted that the action of chemotherapeutic drugs must be considered to be a direct effect of the drug on the parasite and a subsequent activity of the host defence mechanisms on the abnormal parasites, an idea originally proposed by Ehrlich. In addition, a kind of defeatism arose in regard to the chemotherapy of bacterial diseases and this in spite of the fact that a pneumococcic infection in mice had been successfully influenced by a drug as early as 1912 (10).

With the advent of the sulfonamides a considerable amount was added to the principles and methods of chemotherapy. The rapid advance in the sulfonamide field was due mainly to four factors; namely, the fact that bacteria could be readily grown in various media *in vitro*, the fact that invariably fatal bacterial infections could be produced in the mouse by bacteria responsible for important

human infections, the fact that very early quantitative studies of the pharmacology of these drugs was undertaken, and the fact that some sulfonamides are not changed in the body except to be conjugated to their acetyl-derivatives. Aside from improvements in technical methods of study, at least three concepts have emerged from the work done so far in bacterial chemotherapy. These are (*a*) the use of the blood or plasma concentration of drug rather than dosage by mouth to control therapeutic response, (*b*) the demonstration that the best therapeutic effect is obtained by raising blood concentration to the desired level rapidly by giving a large "loading" dose and then giving the drug at frequent intervals, day and night, so as to maintain this blood concentration for several days and (*c*) the development of the idea of metabolite antagonists with the various theories attempting to explain this conception.

Certain workers, including the present writer, believed that the ideas of basing therapeutic response on blood concentration rather than dosage, and of maintaining a more or less constant blood concentration for the best therapeutic effect would represent general chemotherapeutic principles and hold for other drugs and other infections. However, it has been found that this is not so: further discussion can be delayed until we consider malarial chemotherapy.

While possibly adumbrated by several investigators, Woods and Fildes (11, 12, 13) are certainly mainly responsible for furnishing support and giving a broad basis to the concept of metabolite antagonists. According to this concept, the use of chemical compounds structurally related to, but not utilizable in place of, essential metabolites (substances essential in small amount for life or reproduction) interferes with some biological process of a cell or organism and may prevent its survival, growth or reproduction. It is very probable that this essential metabolite antagonism can be explained on a basis of competitive inhibition of some enzyme system. However, regardless of final proof of the mechanism of metabolite antagonism, this general concept appears at present to be one approach to the rational development of chemotherapeutic agents. It has been already extended to parasites other than bacteria. Actual examples of how far this concept has progressed can be found in recent reviews (14, 15, 16, 17).

Of interest in connection with the sulfonamides is the fact that Bell and Roblin (18, 19) proposed a theory which related the structure of sulfanilamide-type compounds to their *in vitro* antibacterial activity. It was suggested that if the antibacterial activity of the sulfonamides is due to competition with p-aminobenzoic acid, then the more closely the competitor compound resembles the metabolite, the greater its activity. In essence, the theory can be stated thus: "the more negative the SO_2 group of an N^1-substituted sulfanilamide derivative, the greater the bacteriostatic activity of the compound." The theory implied that the optimum in antibacterial activity had been reached in sulfadiazine. This appears to be true. However, this theory was based on *in vitro* observations on only *E. coli* and may not apply to other species of bacteria.

The success of the sulfonamides as bacterial chemotherapeutic agents unquestionably stimulated research for the discovery of other antibacterial agents.

The practical development and use of the old idea of antibiosis has been of great importance and has introduced a new concept into the methods used in the search for new chemotherapeutic agents. The discovery of tyrothricin (20), effective against gram-positive organisms but too toxic for systemic use, was of great significance in stimulating a search for this new type of chemotherapeutic agent. The introduction of the penicillins has come very near to fulfilling Ehrlich's dream of an agent toxic to the parasite and completely nontoxic to the host. In addition, streptomycin points the way to the ultimate development of an effective counterpart of the penicillins against gram-negative organisms and the tubercle baccilus.

In the investigation of the penicillins, due possibly to the urgency of wartime, emphasis has been upon the production of the drugs at a reasonable economic figure, the determination of what diseases are favorably influenced by these drugs, and an intensive study of the chemistry of the drugs with a view to synthesis. The results have been magnificent, but with the stress of war removed, one may expect more studies of the chemotherapeutic process to be undertaken.

An extensive cooperative program of research in the chemotherapy of malaria has been carried out during the years 1941–1945. Aside from the fact that this program has yielded results of some practical value in the treatment and suppression of malaria, several new concepts and methods in regard to chemotherapy have been developed and some of our older concepts have had to be radically revised. In the case of bacterial chemotherapy, one can work in the animal with the same species and strains of parasites which cause human diseases and can study infections in a mammal. On the other hand, in the case of the testing of chemical compounds for potential antimalarial activity, one must, at least in initial "screening" tests, work on avian malarial infections. Here, the species of parasites used are quite different from those involved in the human diseases and the host does not even belong to the same Class of animals as man. In addition, the fact that the malarial parasite has a rather complicated life cycle means that antimalarial activity must be studied against sporozoites, cryptozoites (or early tissue stages), exoerythrocytic forms (or late tissue stages) and gametocytes as well as against trophozoites. The enormous amount of quantitative data accumulated in chemotherapeutic studies of avian and human malarias has proved that the suppressive antimalarial activity of a drug in an avian infection may differ markedly from that exhibited in a human infection, and that there seems to be a total lack of correlation between causal prophylactic activity in an avian infection and in vivax malaria in man. In order to "screen" chemical compounds for potential antimalarial activity in man more than one species of avian parasite and more than one avian host must be used (21).

One might object to the above conclusion on the basis that the research which led to the discovery of pamaquine (plasmochin) and quinacrine (atabrine) was carried out entirely on relictum malaria in the canary with the implicit belief that there could be accurate transference from experiments on avian malaria to the human. However, this may be only an example of the fact that luck is still an important factor in the discovery of a good chemotherapeutic agent.

As an example of the importance of the host in chemotherapeutic testing, it has been found that a number of analogues of pantothenic acid are active as antimalarials in gallinaceum and lophurae malarias in the chick, but are inactive in lophurae and cathemerium malarias in the duck. This is an example of successful application of the concept of metabolite antagonists. Apparently, the lack of activity in the duck and activity in the chick are due to the difference in the pantothenic acid content of the two birds. Another analogue of pantothenic acid, pantoyltaurine, is ineffective as a chemotherapeutic agent in streptococcus infections in mice, but is effective in the infections caused by the same organism in rats. Here again, it is known that in rats the concentration of pantothenate in the blood is much lower than in mice (22). It thus appears that if the rational development of chemotherapy proceeds along the lines of metabolite antagonists, it will be extremely important to consider the host factor in attempting to transfer the results of experiments on the lower animals to man.

Until recently, it was generally accepted that in the search for an antimalarial drug, selection could be made on the basis of the chemotherapeutic index determined in an avian infection. On the basis of the work done in this country on antimalarials during the war years (21, 23), it can be definitely stated that the chemotherapeutic index determined in the bird does not correlate at all with the value of a drug as determined in human malaria, and that a large group of compounds, selected as the best from animal tests, must be examined in the human subject for both activity and toxicity in order to obtain the best one for practical use. However, tests on various avian infections for activity and on various species of mammals for toxicity are not only valuable but necessary in order to limit the number of compounds to be tested on man. The necessity for examining a large number of compounds on man is due to the lack of complete correlation between activity in avian tests and that shown in human malarias, and to the fact that the lethal toxicity which is determined in animals is generally not the type of toxicity which limits the maximal dosage for man. For this latter reason, it is doubtful if the chemotherapeutic index of a drug determined in even mammalian experiments can be used as more than a "screening" test for selecting a number of drugs to try in man. Very probably, the correlation of results of animal experiments with those obtained in the human disease in other fields of chemotherapy is not nearly as good as has been assumed; if, in these fields more investigations of activity and toxicity in man could be made, it is probable that much better agents would be discovered.

As has been stated above, investigations in bacterial chemotherapy initiated the important concepts of (*a*) the use of the blood or plasma concentration of drug rather than dosage by mouth as a measure of effectiveness, and (*b*) most effective treatment by maintaining a more or less constant blood concentration of drug, day and night, for several days. These were established as valid for sulfanilamide and certain of its derivatives as chemotherapeutic agents on bacterial infections. However, the tendency has been to extend these concepts to other drugs and other types of infection without proof of their validity under

the new conditions. Unfortunately, evidence has been obtained that these two concepts do not hold as a general principle of chemotherapy. The effectiveness of mapharsen in rabbit syphilis is dependent on the total dosage given, while its toxicity for the rabbit is inversely proportional to the length of time during which a given amount of drug is administered (5). Recently it has been shown that the two concepts mentioned above appear to be valid for the treatment of lophurae malaria in the duck by derivatives of sulfanilamide, but that they do not hold when certain other drugs are used for the treatment of the same experimental malarial infection. Thus, it has been proved that there is a lack of correlation between the plasma concentration of quinacrine and its antimalarial activity in the lophurae infection in the duck (24), and that in the same infection more or less continuous administration of a drug may be equal to, more effective, or less effective than a single daily dose, depending on the drug used (25). Apparently, each individual case of a group of drugs and an infection must be studied in order to determine the most effective and most satisfactory dosage schedule.

It is necessary to point out that despite the emphasis which has been placed in the last decade upon the importance of the blood or plasma concentration of drugs, it is important to realize that certain conditions must be fulfilled before the plasma concentration can be used for the comparison of the therapeutic efficiency of drugs.

In the first place it is essential that any quantitative method for the determination of a drug in plasma, body fluids and tissues should be assessed for its specificity. In addition, it is essential to know if the drug as administered is the only active agent or if it is degraded in the organism to an active compound which is not estimated by the analytical method used.

In the case of sulfanilamide and its derivatives, it is fairly certain that the drug as administered is the active agent and that over 90 per cent of the drug given parenterally can be accounted for by excretion of the drug and its conjugated derivative. However, while the conjugated derivatives of sulfanilamide, sulfapyridine, sulfathiazole and sulfaguanidine have been proved to be the N^4-acetyl derivatives of the parent drugs, this is not so in the case of sulfadiazine (26). Here reasoning by analogy from four drugs to another of the same type leads to error. Comparison on the basis of blood or plasma concentrations is also justified in the case of the sulfonamides because the drugs are or were originally used therapeutically on the basis of blood concentrations. In addition, the blood or plasma concentrations of the sulfonamides, due to the nature of their distribution in the body, represent within a factor of two the total amount of drug in the organism.

Drugs such as quinacrine, chloroquine and a number of other antimalarials differ markedly in their physiological disposition in the organism from the sulfonamides in at least two respects; namely, a marked accumulation in tissues as compared to plasma so that the concentration of quinacrine in certain tissues may be several thousand times that in plasma and the fact that only a small percentage of the administered drug is excreted in a short time, the major

portion being degraded or stored in changed form. One can not transfer to this type of drug the concepts found valid for the sulfonamides. In fact, as stated above, it has been shown that there is no correlation between plasma concentration of quinacrine and antimalarial activity in lophurae infections in the duck.

When antimalarial activity is compared on the basis of plasma concentrations quinacrine is found to be over a hundred times as active as quinine: on the basis of dosage by mouth, quinacrine is only about three times as active as quinine (23). This marked difference is associated with the much higher tissue-plasma distribution ratio of quinacrine as compared to that of quinine. The comparison on a dosage basis would appear to have much more meaning than that based on plasma concentrations.

It is important to emphasize that although under many conditions plasma concentrations do not furnish a satisfactory method for the comparison of drugs, the availability of a method for the estimation of a drug in plasma, body fluids and tissues is almost essential for studying the absorption, distribution, excretion and degradation of the drug. This information is essential in order to make a quantitative pharmacological study of the drug.

The lack of data on the quantitative evaluation of many chemotherapeutic agents in human infection, and in many cases the lack of methods for making quantitative studies precludes detailed discussion of the matter at present. We can, however, discuss the advances that have been made in some of those fields where quantitative studies have been made on man.

Human vivax malaria is a chronic disease and one that is rarely fatal if untreated, and one with good criteria for gauging the results of treatment. However, until the war years quantitative methods for the study of the chemotherapy of the disease scarcely existed. The application of quantitative methods of chemotherapy to malaria was due mainly to Shannon and coworkers (27) and Fairley (28, 29). As an example, in 1942 quinacrine had been in use for ten years and quinine for well over one hundred years, but the relative value of these two drugs in the treatment and suppression of malaria had not been determined. Within a couple of years, quantitative studies proved the superiority of quinacrine over quinine (30). The difficulty in obtaining controlled conditions and satisfactory follow-up in naturally occurring malaria where field studies had to be made was probably partly responsible for the lack of quantitative data. The use on a large scale of experimentally induced human malarial infections, where good control and follow-up could be obtained was necessary for the successful application of modern methods of quantitative chemotherapy to the disease.

In the field of bacterial chemotherapy, quantitative studies of relative activity and toxicity of chemotherapeutic agents have been made on animals, but little data of a quantitative nature are available for the human subject. This is due largely to the fact that the bacterial diseases which are susceptible to chemotherapeutic agents are in general acute diseases with a high mortality rate. This fact precludes applying to these investigations, where for all drugs completely effective doses can be given, a principle which is used for the comparison

of the pharmacological effectiveness of drugs; namely, the use of doses which are only partially effective or only effective in a certain percentage of the individuals treated. In addition, it is obvious that naturally occurring and not experimentally produced infections in man must be used. The relative value of drugs used in the treatment of bacterial diseases has been judged almost entirely by a consideration of the variety of bacteria responding to them, of the speed with which an infection is aborted, and of the nature and extent of the untoward toxic symptoms occurring in the therapeutic use of the drugs. For practical purposes, this may be satisfactory.

As long as only one or two successful chemotherapeutic agents existed for the treatment of any particular infection, it was not of great importance to assess the relative value of these drugs. However, with the advent of a great number of drugs for the treatment of various infections, it became of great importance to attempt to find the most satisfactory agents for each type of infection. This is at the moment an important aspect of chemotherapy and deserves considerable discussion.[3]

The comparison of the relative effectiveness of chemotherapeutic drugs on animals may be made, in general, for one of two purposes; namely, the elucidation of theoretical principles, or "screening" in the animal infection to select the best drugs for trial in man. In regard to the first purpose, the method used will depend on the type of information desired. For instance, if one wishes to attempt a comparison between *in vitro* and *in vivo* activity, the relative *in vivo* activity on the basis of blood or plasma concentrations may be much more informative than a comparison on the basis of dosage. Such has been found to be the case with the sulfonamides (31, 32). If the relative activities of drugs is desired in an animal infection for "screening" purposes, the differences in hosts used must be taken into account as different hosts may differ in respect to the absorption, excretion, distribution and/or degradation of the drug. With the sulfonamides, the host difficulties appear to be eliminated when relative activity is compared on the basis of blood concentrations rather than dosage, but sufficiently accurate quantitative data on human infections with these compounds are not available to be absolutely certain about the matter. A comparison on the basis of blood or plasma concentrations has so far only been made in cases where the blood concentration is maintained more or less constant. In cases where the plasma concentration is not correlated with therapeutic activity, this method can obviously not be used.

With the discovery of large numbers of chemicals with definite chemotherapeutic activities and with the necessity of making quantitative comparisons between these substances, a great increase has occurred in the number of animals used in any experiment. Comparatively few animals are needed to demonstrate presence or absence of therapeutic activity, but in order to compare

[3] This matter would appear to be of most practical importance in the early days of investigation of several remedies with marked therapeutic effect. Time and experience will usually determine the best drug for use. However, advance will be more rapid if some quantitative methods for comparison of activity and toxicity can be used.

several active compounds large numbers may be required. Erroneous conclusions concerning the relative activity and toxicity of a group of compounds have been drawn because of a failure to use for the planning of the experiment and the assessment of the data simple statistical methods, which give an estimate of the errors involved.

Comparisons of the relative activity of drugs in human infections are made also for two purposes; namely, an attempt to correlate activity in the human disease with activity in the experimental animal infection and as an aid in the selection of the most satisfactory drug for use in treatment of that particular human infection. In the first case, if one can make the comparison on the basis of plasma concentrations of drugs, there would appear to be a better chance of a good correlation between the animal and human experiments. However, in many cases this can not be done.

The assessment of the relative value of drugs for the treatment of any particular human infection is frequently an extremely difficult and laborious undertaking. In order to make a comparison of the different drugs in a truly scientific manner, it is necessary to determine for each drug on the human the most advantageous dosage schedule both from the standpoint of therapeutic activity and untoward toxic reactions. This should be done on the basis of dosage and each drug should be used in such a way as to obtain the maximum spread between the effective and toxic dose. This has not, as far as the author is aware, been done as yet for the human but it is certainly a development of the future. In the case of certain antimalarial drugs it has been shown that a single daily dose is more effective than more or less continuous administration in lophurae malaria, while with others there is no difference (25). The toxicity of these same drugs for the rat does not vary in the same way as their antimalarial efficiency when single daily doses are compared with several daily doses (33). Thus, sulfadiazine is much less effective when given as a single dose per day, while quinine and pamaquine are more effective on this dosage regime. Quinacrine is equally effective when given as one dose daily or as several split doses. If the effect on growth of the rat is used as the criterion of toxicity sulfadiazine, quinine and pamaquine possess less toxicity when a given amount of compound is administered once daily than when the same amount is given in fractional doses. If the maximum tolerated doses are considered, these compounds are more toxic when given once daily than in divided doses.

Lastly, a little speculation as to the future of chemotherapy may be permitted. None of the workers in this field would question the great advantage of working on a rational, theoretical basis rather than on the empirical one which has in the main been used hitherto. However, I do not believe the majority of active workers in this field are as sanguine as many scientists who have never worked in the field of chemotherapy of the practical results to be derived from any theoretical basis which can be formulated in the light of the available knowledge of the present time. As far as I know not a single chemotherapeutic agent in clinical use has been discovered as the result of a logical rather than a "hit or miss" approach to the problem. However, it is impossible to agree with the statement of an enzyme chemist who recently stated that as was to be ex-

pected the accomplishments of the empirical method were to date very poor (4). I am inclined to agree with a pharmacologist who recently wrote, "Probably never in the history of medicine has scientific and practical progress in any one field been greater than in chemotherapy during the past 10 years, which are marked by the introduction of the sulfonamides and the antibiotic agents" (34). The acute bacterial diseases have to a large extent been rendered impotent in the last decade. Newer and better antimalarial drugs have been discovered. Recently, one has said that just as the 1880's were the golden age of bacteriology, the present decade is the golden age of chemotherapy (35). However, may I not close on the note that the present decade is only the silver age of chemotherapy, and that the golden age is due in the next decade or two, when physicians can cure a patient "safely, quickly and pleasantly."

The way is already pointing to one great advance in the more practical use of chemotherapeutic agents. This, if accomplished in a practical way, will be a return to Ehrlich's *therapia sterilizans magna*—the complete eradication of the disease by means of a single dose of a drug. While it has been known for a long time that a single dose of drug will cure a trypanosome infection in mice or rats and a syphilitic infection in rabbits, the necessity of many doses of arsphenamine for a cure of human syphilis and the necessity of continuous administration for several days of the sulfonamides in bacterial infections has rather led workers to consider Ehrlich's conception of dosage an unattainable utopia for human disease. We know now, however, that a single dose of penicillins in a streptococcus infection of mice (36) and a single dose of sulfonamide in knowlesi malaria of the monkey (37) will completely eradicate the infections. Also, in the human, a single dose of sulfadiazine will clear up 90 per cent of meningococcus carriers (38) and a single dose of penicillin will cure a large number of individuals infected with gonorrhea (39). In all these cases it is important to realize that success may have been obtained because the parasite is extremely susceptible to the drug and the drug sufficiently non-toxic to be given in such a dose that an effective amount is maintained in the body for a considerable time.

If one examines the data for the susceptibility of different species of the same parasite to drugs, one finds tremendous differences. Thus, different species of bacteria vary widely in their susceptibility to the sulfonamides, the penicillins, and streptomycin; and different species of avian malarial parasites may differ in susceptibility to drugs over 900-fold (40). In addition, there is a marked overlap on different parasites with different chemotherapeutic agents. Thus while emetine and quinacrine appear to be effective only in amoebiasis and malaria respectively, sulfadiazine is effective in both certain bacterial and malarial infections and the penicillins in both bacterial and sypbilitic infections. Does not this suggest that Ehrlich's dream of an agent affecting some receptor of the parasite and none of the receptors of the host's cells may be realized in time for all infectious diseases?

REFERENCES

(1) Ehrlich: Lancet, 2: 445, 1913.
(2) Astwood: Surgery, 16: 679, 1944.

(3) DALE: Physiological Reviews, 3: 359, 1923.
(4) GREEN: Currents in Biochemical Research. Interscience Pub., Inc., New York, 1946 (p. 158).
(5) EAGLE AND HOGAN: Venereal Disease Information, 24: 159, 1943.
(6) DALE AND DOBELL: J. Pharmacol. & Exper. Therap., 10: 399, 1917.
(7) DOMAKG: Ztschr. f. klin. Med., 132: 775, 1937.
(8) DOBELL AND LAIDLAW: Parasitology, 18: 206, 1926.
(9) MARSHALL: Annual Review Physiology, 3: 643, 1941.
(10) MORGENROTH AND LEVY: Klin. Wchnschr., 482: 1560, 1911.
(11) WOODS: Brit. J. Exper. Path., 21: 74, 1940.
(12) WOODS AND FILDES: J. Soc. Chem. Ind., 59: 133, 1940.
(13) FILDES: Lancet, 1: 955, 1940.
(14) WOOLLEY: Science, 100: 579, 1944.
(15) WELCH: Physiological Reviews., 25: 687, 1945.
(16) ROBLIN. Chem. Rev., 38: 255, 1946.
(17) WOOLLEY: Currents in Biochemical Research. Interscience Pub., Inc., New York, 1946 (p. 357).
(18) BELL AND ROBLIN: J. Am. Chem. Soc., 64: 2905, 1942.
(19) ROBLIN AND BELL: Ann. N. Y. Acad. Sci., 44: 449, 1943.
(20) DUBOS: J. Exper. Med., 70: 1, 1939.
(21) MARSHALL: Federation Proceedings, 5: 298, 1946.
(22) MCILWAIN AND HAWKING: Lancet, 1: 449, 1943.
(23) "A Survey of Antimalarial Drugs, 1941–45" sponsored by the Committee on Medical Research of the Office of Scientific Research and Development. F. Y. Wiselogle, editor. J. W. Edwards, Ann Arbor, Mich., 1946.
(24) MARSHALL AND DEARBORN: J. Pharmacol. & Exper. Therap., 88: 142, 1946.
(25) MARSHALL AND DEARBORN: J. Pharmacol. & Exper. Therap., 88: 187, 1946.
(26) KOHN: Proceed. Soc. Exper. Biol. & Med., 59: 21, 1945.
(27) BERLINER, TAGGART, ZUBROD, WELCH, EARLE AND SHANNON: Federation Proceedings, 5: 165, 1946.
(28) FAIRLEY: Trans. Royal Soc. Trop. Med. & Hygiene, 38: 311, 1945.
(29) FAIRLEY: Trans. Royal Soc. Trop. Med. & Hygiene, 40: 105, 1946.
(30) Board for Coordination of Malarial Studies: J. A. M. A., 125: 977, 1944.
(31) LITCHFIELD, WHITE AND MARSHALL: J. Pharmacol. & Exper. Therap., 67: 437, 1939.
(32) MARSHALL, LITCHFIELD, BRATTON, WHITE, AND SHEPHERD: J. Pharmacol. & Exper. Therap., 76: 226, 1942.
(33) SCHMIDT: Personal communication.
(34) MOLITOR: Federation Proceedings, 5: 304, 1946.
(35) AVERY: Trans. Ass. Am. Physicians, 59: 43, 1946.
(36) WHITE, LEE AND ALVERSON: Proc. Soc. Exper. Biol. & Med., 62: 35, 1946.
(37) COGGESHALL: Am. J. Trop. Med., 18: 715, 1938.
(38) PHAIR AND SCHOENBACH: Am. J. Hygiene, 40: 318, 1944.
(39) WELCH, PUTNAM, RANDALL AND HERWICK: J. A. M. A., 126: 1024, 1944.
(40) DEARBORN AND MARSHALL: Am. J. Hygiene, 45: 25, 1947.

THE VIRAL PNEUMONIAS AND PNEUMONIAS OF PROBABLE VIRAL ORIGIN

HOBART A. REIMANN, M.D.

From The Jefferson Medical College and Hospital, Philadelphia, Pa.

CONTENTS

INTRODUCTION

For several decades after 1880, pneumonia was named and classified on a pathologic-anatomic basis. With the gradual establishment of a number of bacterial pneumonias as clinical entities, an improved method of etiologic diagnosis came into vogue about 1920. Little attention, however, was given to the filtrable viruses as causes of pneumonia despite the progress made in the knowledge of diseases caused by dermatotropic and neurotropic viruses. Several reasons for the lag of interest in pneumonotropic viruses may be cited as follows: (a) the high incidence and mortality rate of the bacterial pneumonias demanded precedence of interest, (b) the viral infections of the respiratory tract by contrast were of lesser importance, (c) studies were hampered by technical difficulties of research on viruses and a lack of suitable experimental animals, (d) the pulmonary lesions of viral infections are often obscured at necropsy by bacterial invasion, and (e) many pulmonary lesions were undetected because roentgenography in the past was not generally used in mild diseases. Yet now and then, report was made of peculiar forms of pneumonia which were obviously infectious but not associated with visible or cultivable bacteria.

As early as 1861, Bartels described the pathology of interstitial pneumonia during an epidemic of measles. Delafield studied idiopathic bronchopneumonia in 1884, in 1898 Koester (35) suspected the pneumonia of measles to be an integral part of the disease, and in 1903 Bose (8) and Borrell (7) both described sheep-pox pneumonia characterized by a mononuclear cell infiltration which they thought to be neoplastic. Bose described an unusual form of pneumonia in rabbits inoculated with vaccine virus. Guarnieri bodies were found in the lung of smallpox by Keysselitz and Mayer in 1909, and Alagna recorded specific histologic changes in

the lungs during measles in 1911. Pneumonia characterized by an exudate of mononuclear cells was described in 1927 by Cowdry (11) in chronic pneumonias of sheep, called jaagziekte and Montana progressive pneumonia. Interest in the subject was greatly stimulated during the pandemic of influenza in 1918, especially by MacCallum. At that time Goodpasture described instances of bacteria-free pneumonia. Further evidence of the etiologic relation of the viruses of smallpox and vaccinia to pneumonia came from the experiments of Levaditi and Guerin in 1923, of Lillie and Armstrong in 1924, and of McCordock and Muckenfuss in 1933 in whose papers are references to many older studies.

In the pneumonias to be discussed in the following pages, the viruses are for the most part airborne and enter through the respiratory tract. In some, such as measles or psittacosis, the lungs are involved as an incident in a generalized infection with predominant signs and symptoms elseswhere; in others like influenza, the infection appears to involve the respiratory tract primarily. The lungs actually are involved much more often in most of these infections than is generally realized but the pneumonia is seldom of clinical significance. The first part of this review deals with pneumonias in diseases caused by known viruses, which, except for influenza, are now relatively uncommon; and some are only of academic interest. They serve as a background for the second part which deals more extensively with the syndrome of current interest commonly called "primary atypical pneumonia of unknown cause", or "viral pneumonia" as many prefer, at some risk of error, since proof of its viral origin is incomplete. Pneumonias caused by bacteria of the pleuropneumonia group, by toxoplasmas, by Coccidioides immitis and by rickettsia, although clinically and pathologically similar to viral pneumonias are not included for discussion here.

PART I

PNEUMONIAS OF VIRAL ORIGIN

Measles Pneumonia

Koester (35) and Feyrter (18) believed the pneumonic infiltration during measles to be a specific reaction to the causative agent. Milles (45) who briefly reviews the literature also regards pneumonia not necessarily as a complication but as an integral part of the disease. Pneumonia is recorded as occurring in 12 per cent of patients with measles (9, 60) but without routine roentgenography and necropsy study it is impossible to discover its true incidence or to tell if it is caused primarily by the virus, by secondary bacterial invasion or by bacteria alone. The incidence of pneumonia is actually much higher.

Kohn and Koiransky (36) reported some of the earliest roentgenographic studies of the chest of children in the preëruptive or eruptive stages of measles. Abnormal density of the broncho-pulmonary markings was seen in 80 per cent of 130 cases. Shadows suggesting infiltration of the lung were seen at some time during the course in one-half of the patients, especially in children under the age of 4. Infiltration of the interstitial peribronchial area spread to the adjacent alveolar parenchyma in the early eruptive stage. The description of the shadows

is identical with that of other viral pneumonias. As in viral pneumonias of unknown cause, the physical signs of pneumonia were absent in half of these patients and the pneumonic process first appeared or continued to evolve after the patient had recovered clinically. The clinical course usually was more severe, and fatalities occurred only in patients with evidence of pulmonary involvement. Shadows persisted from 2 to 4 weeks in some instances. The hilar lymph nodes were seldom enlarged. In Milles' (45) studies, roentgenographic evidence of pneumonia appeared in 62 per cent of 61 children with measles, and in only 15 per cent was pneumonia diagnosed by physical signs alone. Similar findings were recorded in England (24) where roentgenographic evidence of pulmonary infiltration and increased density of the broncho-vascular markings were visualized in 55 per cent of patients, often in the preëruptive stage, favoring the view that the virus alone causes pneumonia.

Although the gross and histologic reaction of the lung as described by Bartels and others resembles that of other viral pneumonias, Alagna discovered the specific giant cell which now bears his name. These large cells with 8 to 15 nuclei, together with small firm nodules were also found by others. Corbett (10) describes giant cells of the Warthin-Finkeldey type in the peribronchial tissue, suggests their probable specificity for measles and discusses the pertinent literature. There often is evidence of secondary bacterial invasion late in the disease.

Variola Pneumonia

Pneumonia is a serious occurrence in smallpox and for years when the disease was a common one, it was regarded principally as bacterial in origin since at necropsy the lungs, like the skin, were invaded secondarily with pyogenic bacteria. Pustules in the upper and lower airways, hemorrhages in the lungs and pneumonia were repeatedly described in studies at necropsy (38, 39), but despite the presence of Guarnieri bodies in the lungs, little attention was given to the specificity of the changes.

Lillie and Armstrong (38) produced pulmonary lesions identical with those of smallpox pneumonia in rabbits inoculated with vaccine virus. The perivascular changes, proliferative and infiltrative lesions composed chiefly of mononuclear cells and areas of focal necrosis were the same as those found in other viral pneumonias. Later in the course of the disease, the lesions were modified and obscured by mixed bacterial invasion. According to Lillie (39) the pneumonia of variola is caused primarily by the virus itself and, like the dermal lesions, is modified by the invasion of bacteria.

In a small outbreak of variola 7 persons, who did not have smallpox, developed the signs and symptoms of viral pneumonia between the eleventh and fifteenth day after contact with patients. The pneumonia supposedly was caused by the virus of smallpox (32).

Vaccinia Pneumonia

Peribronchial inflammatory areas of mononuclear and polymorphonuclear cells, alveolar hemorrhage, edema and atelectasis appeared in the lungs of animals

injected intravenously with vaccinia neurovaccine by Levaditi and Nicolau. Other investigators reported similar results, but most attention was given to the lungs by Lillie and Armstrong (38) who inoculated rabbits intranasally and intratracheally with vaccine virus. Bacteria-free pneumonia developed as early as 26 hours later. The inflammatory reaction consisted chiefly of mononuclear cells and proliferation except where necrosis or secondary bacterial invasion took place. Inclusion forms resembling Guarnieri bodies were found in the alveolar epithelial cells. The lesions of vaccinia and variola were alike, differing only in degree of severity. Similar changes were recorded by McCordock and Muckenfuss (42) who described 2 kinds of early reaction. A large inoculum caused a hemorrhagic pneumonia and a smaller amount of virus, or virus inoculated in partially immunized rabbits, caused an interstitial involvement with a mononuclear cell reaction, typical of most viral pneumonias. Cytoplasmic inclusions resembling Guarnieri bodies often were found in the bronchial epithelium. Bacterial invasion occurred in the late stages. Not all strains of vaccinia virus cause pneumonia (47).

Varicella Pneumonia

Waring and his associates (71) described 2 cases of severe chickenpox with pneumonia in adults. Both had symptoms of pneumonia and widespread mottling in both lungs in roentgenograms. One patient died. Necropsy revealed extensive encephalitis and hemorrhagic pneumonia, the latter characterized by an exudate composed chiefly of mononuclear cells, proliferation of the septal cells, a prominent alveolar lining, necrosis of the alveolar walls, and injury to the blood vessels. Bacteria were rare or absent. A similar case was described by Rausch and his coworkers (59). A case of varicella neonatorum with pneumonia was observed (40a).

The Pneumonia of Lymphocytic Choriomeningitis

Smadel and his associates (64) reported 2 fatal cases with severe systemic disease and pneumonia caused by the virus of lymphoctytic choriomeningitis but without the usual neurologic signs or symptoms. The diagnosis was made postmortem after the virus was recovered from the lungs. There was an interstitial pneumonia with exudate, in some areas composed wholly of mononuclear cells. Similar cases were reported by others referred to by Hayes and Hartman (28). Pulmonary lesions commonly occur in experimentally infected animals and if sought for would probably be found more often in human cases. The literature is reviewed by Farmer and Janeway (16).

The occurrence of encephalitis and pneumonia in varicella together with recognition of pulomonary involvement in lymphocytic choriomeningitis shows that certain viruses may be dermatotropic, neurotropic and pneumonotropic. They may attack the myocardium (20). Pneumonia also occurs during postvaccinal encephalitis (70). However, in comatose patients it is impossible to differentiate viral pneumonia from aspiration pneumonia of other cause without pathologic and etiologic proof.

Influenzal Pneumonia

Little has been added to the knowledge of influenzal pneumonia since recent reviews of the subject were made (19, 60, 61, 62, 67). A virus was suspected to be the cause of influenza by a number of investigators during the pandemic in 1918 when bacteria-free, interstitial pneumonia was encountered in a few instances at necropsy. The issue usually was clouded late in the disease by the secondary invasion of bacteria, particularly of pyogenic cocci (41). The problem was clarified by the discovery of the virus of influenza A by Smith, Andrewes and Laidlaw in 1933, and of the B virus soon afterward by Francis and Magill. Since influenza is now recognized as an etiologic entity and since pulmonary involvement is an integral part of it, the term influenzal pneumonia should be restricted to the pneumonias caused by the viruses of influenza A or B, and not to complicating bacterial pneumonias, nor to the pneumonia caused by the misnamed influenza bacillus (Hemophilus influenzae or Pfeiffer's bacillus). For unknown reasons influenzal lesions of the lung in man and in animals more often are invaded by pneumococci, staphylococci, hemolytic streptococci and Pfeiffer's bacilli than the viral pneumonias discussed in a later section.

The viruses of influenza A and B, and perhaps of certain forms not yet classified, cause disease clinically indistinguishable from each other and from other mild infections of the respiratory tract (26, 27, 246). Differentiation can be made only by the isolation and identification of A or B virus or of evidence of their operation by the chicken erythrocyte agglutination test 7, the demonstration of specific neutralizing antibodies or by fixation of complement. In some proved cases of influenza, demonstrable serologic evidence of infection fails to appear.

The influenza viruses primarily attack the mucous membrane of the respiratory tract. Inoculated mice almost invariably develop pneumonia, and in those infected by inhalation, pneumonia occurs without involvement of the nasal and pharyngeal epithelium (40). In man, the upper airways are involved chiefly, but any part of the tract may be affected. Attacks vary in severity as (a) asymptomatic, inapparent infections which are indetectable except by serologic means, (b) mild ambulatory forms, (c) mild forms with pneumonia, (d) severe forms without pneumonia, and (e) severe forms with pneumonia. The degree of clinical severity is usually proportionate to the extent and intensity of the involvement, which in turn may be dependent upon the amount and kind of toxin made by the infecting strain of virus (30). Attacks of influenza vary in severity according to the characteristics of the rampant strain, and/or upon the variable resistance of the host. Attacks in some outbreaks are all mild; in others, severe pneumonic forms are common. The incidence of pneumonia as reported in patients varies clinically and roentgenographically in different epidemics as follows:

Adams (1)	None in *Influenza A*
Hare (26)	None in *Influenza B*
Nigg (49)	1 % in *Influenza B*
Hare (26)	20% in *Influenza B*
Pollard (54)	28% in *Influenza A*
Stuart-Harris (67)	61% in *Influenza A*
Scadding (61)	70% in *Influenza A*

According to Scadding (61) and Stuart-Harris (67), and in contrast with the viral pneumonias discussed in later pages, the extent of the lesions visualized roentgenographically usually was less than would have been expected from the nature of the physical signs.

Pathologically, the mucosa of different parts of the respiratory tract may be involved independently at different times or all at once. Unfortunately, no one has reported histologic studies of the upper respiratory passages in fatal cases. Adams (2) reported studies of swab preparations from the pharynx of patients during influenza A which revealed large sloughed-off sheets of epithelial cells and an exudate of mononuclear cells. In one case complicated with staphylococcal invasion (53) the mucous membrane from the trachea to the tertiary bronchi was covered by an exudate overlying an intensely congested surface. The epithelium of the trachea was completely destroyed. In animals, histologically, there is necrobiosis, desquamation and fibroid necrosis of the epithelium with denudation of the surfaces, and inflammation in the submucosa (20, 23, 31).

The pneumonia is similar in animals and in man. It is intersititial in kind, like that of other viral infections, and is characterized by proliferation and an exudate of mononuclear cells. There is secondary dilation of the bronchioles with edema, hyperemia and collapse of alveoli, leading to areas of atelectasis and/or emphysema. A hyaline membrane may line the alveoli (53). As stated before, the pulmonary lesion is often obscured by coccal invasion.

In Finland's (21) series of 24 cases of pneumonia during and after an outbreak of influenza A, Pneumoccoccus was obtained from the lungs in 12, Staphylococcus aureus from 5, both pneumococci and staphylococci from 1, and in 1 only a few alpha hemolytic streptoccocci were present. Leukopenia occurred in many of the patients and antibodies for influenza A were present in all. In five other cases studied at necropsy (53) coccal invasion was present in 3 and bacteria-free pneumonia in 2. Jackson (33) reported pneumonia presumably pneumococcal in origin in 14 per cent of patients with influenza B. Invasion of the lungs with staphylococci is especially common in some epidemics.

Pneumonias Caused by Viruses of the Psittacosis Group

Pneumonias caused by this group of agents are included for review because these microorganisms, like viruses, are filtrable and the epidemiologic, clinical and pathologic characteristics of the pneumonias they cause are like those of certain other viral diseases. Yet these agents apparently comprise a biologic group midway between viruses and rickettsia in the evolutionary scale since they consist of, or are regularly associated with, characteristic microscopically visible elements. They are also susceptible in some degree to sulfonamide compounds and to penicillin.

Older literature on the pneumonias of the psittacosis group is reviewed elsewhere (17, 19, 60). Interest in these infections has grown rapidly since the viral pneumonias came into prominence after 1938, and after the discovery by Pinkerton and Swank of a virus causing a disease of pigeons later named ornithosis by Meyer (44). Up to the present at least 15 pneumonia-producing agents have

been isolated in widely separated parts of the world from human beings, animals and birds, as shown with their respective hosts in the accompanying list. Most of the agents have been encountered during attempts to discover the etiology of viral pneumonias of unknown cause.

Psittacosis	bird, human	Meningopneumonitis virus (22a, 46)	ferret, human
S-F Virus (46)	human	Pneumonitis virus (50, 51)	mouse
Ornithosis (44)	bird, human	Australian virus (12)	mouse
W-ornithosis (54a)	marine birds	Virus of Gönnert (25)	mouse
Fulmar disease (58)	bird, human	Virus of Karr (34)	mouse
Ailourosis (4)	cat, human ?	Intranuclear inclusion agent (66)	pigeons
Louisiana pneumonitis (37)	human	Heartwater fever agent ? (57)	sheep
Illinois virus (74)	human		
Lymphogranuloma venereum (73)	human		

In 1934, Francis and Magill (22a) isolated mouse meningopneumonitis virus from mice inoculated with exudates from patients with undifferentiated mild infections of the respiratory tract. Identical or related agents were later found in mice inoculated with patients' sputum by Eaton and his coworkers (13) who later (46) reported a case of human infection, and by Gönnert (25), Nigg (50, 51), Karr (34) and DeBurgh (12).

Infections in mice caused by these agents differ from those of influenza viruses and from the PVM virus to be discussed in a later section. They cause systemic disease, result in a carrier state, and more often cause death after intranasal inoculation (51). Focal or patchy grey lesions appear in the lungs.

It is uncertain at present if the agents of psittacosis, ornithosis, S-F disease, Fulmar disease and others are identical (55), or are variant forms of each other or of a common parent form becoming differentiated by residence in different hosts, or if they represent separate fixed types (46). They may be distinguished to some extent by their sources and by their different effects in experimental animals and birds. The complement fixation test is of no value in differentiating the agents from each other, and is of doubtful value in differentiating them from other agents because of the frequent reactions with dissimilar antigens which occur in the serum from patients with these infections (100).

Several other similar or related agents have been discovered. A virus which causes pneumonia in cats (4), probably the cat distemper of English observers, was also suspected of infecting humans in contact with sick cats. The virus is different from the virus Howard (77) isolated from cats and is related to the psittacosis group (68). Because of the precedent set in naming other related agents of this group, the term ailourosis for it was proposed (243). An outbreak of severe pneumonia occurred in Louisiana caused by a psittacosis-like virus (37) and a similar agent called the Illinois virus was isolated in Chicago (74). A case of pneumonia probably caused by the agent of lymphogranuloma venereum was reported (73). A virus called the intranuclear inclusion (I.N.I.) agent, different from psittacosis or ornithosis, was isolated from pigeons (66).

Evidence of an ornithosis-like injection is present in a variety of marine birds (54a). It is suggested that the agent of heartwater fever of sheep formerly regarded as a rickettsia belongs in the psittacosis group of viruses (57). It is obvious that much work is needed to bring about order among the numerous microbes discussed, as to their relationship with each other and their relationship to human disease.

Early studies suggested that agents of this group may cause a considerable proportion of cases of viral pneumonia (14, 17, 63, 242) but they probably account for only a small percentage (83). They were not encountered at all in a group of 500 viral pneumonias (141d).

So far as is known, infections in man, excepting lymphogranuloma venereum, are usually pneumonic and severe with a mortality rate of about 10 per cent. They are contracted for the most part by close contact with sick birds or animals (17, 46) or by inhaling their dried secretions or excrement (48). The evidence in a few instances of apparent person to person contact (37, 46) suggests other means of infection, probably by exhaled droplets. The occurrence of pneumonia in lymphogranuloma venereum points to venereal transmission. The attacks usually occur as isolated sporadic cases or groups of mostly severe cases close to a source of infection, usually birds (44, 58, 65) and probably rodents (46), cats (4) and man (46). Laboratory infections are common. Attacks occur in persons who have no discoverable contact with known sources, suggesting contact with human carriers (242) who are known to exist (44a).

Clinically, roentgenologically and pathologically the pneumonias resemble the severest forms of the commonly occurring viral pneumonias (17, 233, 242) as described on later pages. According to Rake, a powerful toxin made by certain of the agents is partly responsible for the symptoms. The diagnosis is aided by epidemiologic factors of contact, and the absence of a cold agglutinin and of agglutinin for streptococcus MG in the serum. The complement fixation test, as just stated, is unreliable as a diagnostic aid (100), but a sharp rise and subsequent fall in the titer in early convalescence adds supportive evidence (14, 15). Diagnosis is established only by the isolation and identification of the causative agents (46).

The pulmonary pathology is characterized by an interstitial form of pneumonia with an exudate chiefly composed of mononuclear cells, and is indistinguishable from many other viral pneumonias (17, 43), except for the presence of minute coccoid bodies, called "Rickettsia psittaci" by Lillie, in large phagocytic cells and in mononuclear cells present in the alveolar walls. Experimentally the agent of Louisiana pneumonia virus caused generalized vascular lesions like those of rickettsial infections. Intranasal inoculation caused a pneumonic process with coccoid bodies which in contrast with certain other viral or rickettsial infections, was not accompanied by bronchial involvement (22).

In experiments on animals (56), sulfonamide compounds control infections but proportionate dosage in man would probably be toxic. Penicillin was successfully used in infected animals (29) and apparently so in a few patients (44a, 52, 69).

PART II. PNEUMONIAS OF PROBABLE VIRAL ORIGIN

Pneumonia in Infectious Mononucleosis

Most observers regard infectious mononucleosis as a viral disease which it indeed appears to be except for final proof. In one series of 500 cases, pneumonia was detected in 14 per cent (277). The pneumonia is rarely a dominant clinical feature and is indistinguishable from other viral pneumonias except for the peculiarities of the disease itself. In several patients the disease was mild in spite of extensive pulmonary involvement as demonstrated roentgenographically. One of these was nearly afebrile. The pneumonia may be caused by the same agent or by a concurrent infection. The authors observed a rise in the heterophile agglutinin titer, characteristic of infectious mononucleosis, in several patients with primary atypical pneumonia of unknown cause (viral pneumonia) yet no abnormal leukocytes or mononucleosis appeared. A similar circumstance was noted by Young, Storey and Redmond (234) and by Adams (104). The latter recorded a positive heterophile antibody reaction in 18 of 50 cases of the common form of viral pneumonia. Whether the reaction occasionally occurs in viral pneumonia, whether the diseases are related or overlap or whether a different etiologic entity was encountered cannot be said at present.

Pneumonia of Erythema Multiforme Exudativum

Pneumonia was demonstrated in 14 to 17 cases of erythema multiforme exudativum (129 b). It is characterized by a mononuclear cell exudate like viral pneumonia, and is believed to be an integral part of the disease which is presumably caused by a virus. The disease resembles the human foot and mouth disease and may be mistaken for Vincent's infection because of the presence of fusospirochetal microörganisms in the oral lesions. It is called dermatostomatitis, mucocutaneous fever, mucosal respiratory syndrome, and is probably the same as Stevens-Johnson disease (129a). It is probable that certain cases diagnosed as viral pneumonia with severe mucocutaneous eruptions are actually those of the disease in question (205).

Viral Pneumonias of Infants

Two forms of pulmonary infections described in infants have been tentatively called viral pneumonias because of their resemblance to known viral pneumonias, yet their cause is unknown. Goodpasture and his associates (166) studied a form of pneumonia which often follows certain infectious diseases. Intranuclear inclusion bodies characteristic of many viral diseases were found almost exclusively in the epithelial cells of the respiratory tract. The infection is not caused by the virus of herpes simplex nor is it related to the socalled inclusion disease of infants.

Adams (105) reported 3 epidemics of primary "virus" pneumonitis in infants during a period of 4 years. All 3 epidemics occurred in Minnesota and similar ones have been observed elsewhere but have not been reported. The disease appears to be viral in origin because of its epidemiology, clinical behavior, the

presence of cytoplasmic inclusion bodies in the epithelial cells of the upper respiratory passages with sheets of sloughed-off epithelial cells and a mononuclear cell exudate, as found during influenza (2). Inclusion bodies are also present in the bronchial, bronchiolar and alveolar cells, and the pneumonia is interstitial in kind. The mortality rate is reported as 20 per cent, but subsequent studies indicate that many heretofore unrecognized mild pneumonic forms of the same disease probably exist. Furthermore, the infection may be related to mild disease of adults, particularly of the mothers, who occasionally had mild disease of the respiratory tract with similar inclusion bodies in the epithelial cells at the time the infants were sick. Ingleby (185) reported similar inclusion bodies in the lungs and brain of adults with pneumonia and encephalitis.

Pinkerton and his associates (232) described a still different kind of giant cell pneumonia in infants characterized by interstitial pneumonia with large multinucleated cells and cytoplasmic inclusion bodies in the epithelial cells. No nuclear inclusions were seen. Histologically the changes resemble those found in measles and in distemper in dogs. They may be specific or may be caused by various agents (10).

Pneumonias in Undifferentiated Mild Infections of the Respiratory Tract; Primary Atypical Pneumonia of Unknown Cause; Viral Pneumonias

The pneumonias described in part I represent primary infections of the lung or respiratory tract, or pulmonary involvement incident to systemic diseases caused by various known filtrable viruses. The assumption that other, still unidentified forms of viral pneumonia exist (60) has been borne out during the past 10 years. These "new" pneumonias emerged from obscurity for several reasons: (a) because of the great reduction in the number of the severe bacterial pneumonias by sulfonamide chemotherapy and penicillin which allowed attention to be given to the milder varieties, (b) their establishment as entities, (c) the more frequent use of roentgenography, and (d) because of the increase in the number of viral pneumonias in epidemics particularly among the armed forces during World War II. It became evident that many mild forms of pneumonia previously had been unrecognized, ignored or misdiagnosed as of bacterial origin, or called atelectasis, bronchopneumonia, bronchitis, bronchiolitis, threatened pneumonia, a touch of pneumonia, congestion or a spot on the lung. Their differentiation from influenza and the suggestion of a probable etiologic role of other viruses still unknown opened a new field for study (239). The discussion in the following pages deals with these newly recognized pneumonias.

At the outset it must be made plain that these pneumonias comprise a syndrome probably composed of a number of entities caused by similar or dissimilar, related or unrelated agents. Routine roentgenography of large numbers of ambulatory people, especially of those with mild disease of the respiratory tract (109, 118, 120, 156, 238, 317) discovers many otherwise unsuspected transitory pulmonary lesions. Pneumonia is reported (246) in 12 to 15 per cent of patients with the common cold, exudative pharyngitis and febrile catarrh.

Without other studies, it is impossible, of course, to decide whether the pneumonia is caused by the same agent responsible for the mild disease, how much of the shadow may be caused by atelectasis or if it is caused by bacterial invasion. It is, however, believed to be an integral part of the infection in many instances. Studies by the Army Commission (129) revealed pneumonia in several soldiers with exudative pharyngitis of unknown cause, but different from the common cold. Furthermore, numerous filtrable agents have been encountered during etiologic studies and although none has been decisively established as the cause, it seems most likely from general evidence that one or more viruses are the etiologic agents (141, 183, 243, 272). Therefore, during this period of uncertainty, the group of pneumonias presumably of viral origin may be discussed together as a syndrome because the clinical symptoms and signs and the pathologic changes as described are common to all. It must also be noted that many observers, in discussing the syndrome, dealt only with the pneumonic forms and excluded the mild nonpneumonic or the afebrile attacks which in all probability are of the same cause and at times constitute the majority of cases in various widespread, epidemic infections of the respiratory tract.

History. Reviewers of the subject (140, 144) and others (Libman, Cole, 142) have resurrected clinical and pathologic descriptions of pneumonia resembling the kinds discussed here studied as early as 1812, but especially during the Civil War years. Without doubt, Bartels, Woillez, Leichtenstern, Delafield, MacCallum and others included what are now called viral pneumonias in their observations, but it is impossible to make retrospective diagnoses or to extricate them from the pneumonias of measles, influenza, and others. Nor can certain descriptions of similar diseases published about the time of the 1918 pandemic of influenza be separated from influenza. Between 1920 and 1935 numerous European physicians were well aware of transient pulmonary involvement during minor respiratory tract disease as discovered by roentgenography. Their reports are summarized by Ramsay and Scadding (238) and others (140, 144). After this time, almost all contributions to the knowledge of the disease were made by American physicians.

In 1930, Arrasmith (111) reported a series of patients with "influenzal" pneumonia. Gallagher (159) in 1934, described epidemics of bronchopneumonia in youths, which were different from other kinds of pneumonia. Bowen (120) in performing routine roentgenography on 1750 persons with mild infections of the respiratory tract, discovered 89 cases of "acute influenzal pneumonitis" which he regarded as a complication of influenza. Allen (107) with Bowen's roentgenologic aid in 1936, reported similar observations and believed the pneumonia to be caused by a virus and secondary bacterial invasion. Cass (125) was concerned with the pulmonary involvement during "influenza" in 1936, and in the next year, Scadding (252) described cases of disseminated focal pneumonia and Wall discussed interstitial pneumonia (276a). Bock (118) in 1938, dealing with epidemic mild infections of the respiratory tract, incidentally referred to a group of cases named as possible virus pneumonia. In the same year Gill (162) reported several instances of pneumonitis. While it is almost

presence of cytoplasmic inclusion bodies in the epithelial cells of the upper respiratory passages with sheets of sloughed-off epithelial cells and a mononuclear cell exudate, as found during influenza (2). Inclusion bodies are also present in the bronchial, bronchiolar and alveolar cells, and the pneumonia is interstitial in kind. The mortality rate is reported as 20 per cent, but subsequent studies indicate that many heretofore unrecognized mild pneumonic forms of the same disease probably exist. Furthermore, the infection may be related to mild disease of adults, particularly of the mothers, who occasionally had mild disease of the respiratory tract with similar inclusion bodies in the epithelial cells at the time the infants were sick. Ingleby (185) reported similar inclusion bodies in the lungs and brain of adults with pneumonia and encephalitis.

Pinkerton and his associates (232) described a still different kind of giant cell pneumonia in infants characterized by interstitial pneumonia with large multinucleated cells and cytoplasmic inclusion bodies in the epithelial cells. No nuclear inclusions were seen. Histologically the changes resemble those found in measles and in distemper in dogs. They may be specific or may be caused by various agents (10).

Pneumonias in Undifferentiated Mild Infections of the Respiratory Tract; Primary Atypical Pneumonia of Unknown Cause; Viral Pneumonias

The pneumonias described in part I represent primary infections of the lung or respiratory tract, or pulmonary involvement incident to systemic diseases caused by various known filtrable viruses. The assumption that other, still unidentified forms of viral pneumonia exist (60) has been borne out during the past 10 years. These "new" pneumonias emerged from obscurity for several reasons: (a) because of the great reduction in the number of the severe bacterial pneumonias by sulfonamide chemotherapy and penicillin which allowed attention to be given to the milder varieties, (b) their establishment as entities, (c) the more frequent use of roentgenography, and (d) because of the increase in the number of viral pneumonias in epidemics particularly among the armed forces during World War II. It became evident that many mild forms of pneumonia previously had been unrecognized, ignored or misdiagnosed as of bacterial origin, or called atelectasis, bronchopneumonia, bronchitis, bronchiolitis, threatened pneumonia, a touch of pneumonia, congestion or a spot on the lung. Their differentiation from influenza and the suggestion of a probable etiologic role of other viruses still unknown opened a new field for study (239). The discussion in the following pages deals with these newly recognized pneumonias.

At the outset it must be made plain that these pneumonias comprise a syndrome probably composed of a number of entities caused by similar or dissimilar, related or unrelated agents. Routine roentgenography of large numbers of ambulatory people, especially of those with mild disease of the respiratory tract (109, 118, 120, 156, 238, 317) discovers many otherwise unsuspected transitory pulmonary lesions. Pneumonia is reported (246) in 12 to 15 per cent of patients with the common cold, exudative pharyngitis and febrile catarrh.

Without other studies, it is impossible, of course, to decide whether the pneumonia is caused by the same agent responsible for the mild disease, how much of the shadow may be caused by atelectasis or if it is caused by bacterial invasion. It is, however, believed to be an integral part of the infection in many instances. Studies by the Army Commission (129) revealed pneumonia in several soldiers with exudative pharyngitis of unknown cause, but different from the common cold. Furthermore, numerous filtrable agents have been encountered during etiologic studies and although none has been decisively established as the cause, it seems most likely from general evidence that one or more viruses are the etiologic agents (141, 183, 243, 272). Therefore, during this period of uncertainty, the group of pneumonias presumably of viral origin may be discussed together as a syndrome because the clinical symptoms and signs and the pathologic changes as described are common to all. It must also be noted that many observers, in discussing the syndrome, dealt only with the pneumonic forms and excluded the mild nonpneumonic or the afebrile attacks which in all probability are of the same cause and at times constitute the majority of cases in various widespread, epidemic infections of the respiratory tract.

History. Reviewers of the subject (140, 144) and others (Libman, Cole, 142) have resurrected clinical and pathologic descriptions of pneumonia resembling the kinds discussed here studied as early as 1812, but especially during the Civil War years. Without doubt, Bartels, Woillez, Leichtenstern, Delafield, MacCallum and others included what are now called viral pneumonias in their observations, but it is impossible to make retrospective diagnoses or to extricate them from the pneumonias of measles, influenza, and others. Nor can certain descriptions of similar diseases published about the time of the 1918 pandemic of influenza be separated from influenza. Between 1920 and 1935 numerous European physicians were well aware of transient pulmonary involvement during minor respiratory tract disease as discovered by roentgenography. Their reports are summarized by Ramsay and Scadding (238) and others (140, 144). After this time, almost all contributions to the knowledge of the disease were made by American physicians.

In 1930, Arrasmith (111) reported a series of patients with "influenzal" pneumonia. Gallagher (159) in 1934, described epidemics of bronchopneumonia in youths, which were different from other kinds of pneumonia. Bowen (120) in performing routine roentgenography on 1750 persons with mild infections of the respiratory tract, discovered 89 cases of "acute influenzal pneumonitis" which he regarded as a complication of influenza. Allen (107) with Bowen's roentgenologic aid in 1936, reported similar observations and believed the pneumonia to be caused by a virus and secondary bacterial invasion. Cass (125) was concerned with the pulmonary involvement during "influenza" in 1936, and in the next year, Scadding (252) described cases of disseminated focal pneumonia and Wall discussed interstitial pneumonia (276a). Bock (118) in 1938, dealing with epidemic mild infections of the respiratory tract, incidentally referred to a group of cases named as possible virus pneumonia. In the same year Gill (162) reported several instances of pneumonitis. While it is almost

certain that all of these observers dealt with certain kinds of viral pneumonia as it is now regarded, there was no way of differentiating them from the pneumonias of influenza until after the discovery of the virus of influenza in 1933 and the development of diagnostic tests for it several years later. None of the authors emphasized the establishment of a separate, newly recognized syndrome, none reported attempts to discover the cause, and their publications failed to arouse interest.

In 1938, Reimann (60, 239, 240) observed a number of pneumonias which could not be classified with known entities, grouped them as comprising a newly recognized syndrome under the names atypical pneumonia or virus pneumonia; initiated studies which led to the isolation of an elusive filtrable agent; described the characteristic clinical course, roentgenographic changes, the paucity of complications and the ineffectiveness of sulfonamide therapy; predicted the nature of the pathologic changes; and suggested that these pneumonias represent either severe, sporadic isolated cases, or the severe pneumonic forms of mild, epidemic disease of the respiratory tract. The observations were confirmed in a rapid succession of reports by Smiley and his associates, Rainey, Maxfield, Murray, Kneeland, Longcope and many others thereafter.

Terminology. Plummer and Ensworth (233) have gathered 25 names given to the disease to which may be added silent bronchopneumonia (109), sulfonamide resistant pneumonia (170), nonbacterial pneumonia, and viroid (245). The names most commonly used are atypical pneumonia, primary atypical pneumonia of unknown cause, viral or virus pneumonia, bronchopneumonia and acute pneumonitis (207). Each author prefers his own selection, but none is wholly satisfactory. The term nonbacterial pneumonia cannot be used safely until the position of indifferent streptococci as possible etiologic factors is clarified. The term primary atypical pneumonia, etiology unknown, as adopted by the Surgeon General of the Army (224) if used in its entirety is adequate but cumbersome. Unfortunately, it is usually contracted to "atypical pneumonia" which is regarded as meaningless and misleading (272). This term, even with the adjective "primary," is so broad as to include any pneumonia not conforming clinically with classic pneumococcal lobar pneumonia, the prototype of "typical pneumonia" as proposed by Cole (127). Primary atypical pneumonias in this sense include the pneumonias of tuberculosis, coccidioidomycosis, Q fever and many others of known and unknown origin. The term is a negative one and its use has already led to such ambiguous combinations as "atypical atypical" pneumonia (179), "typical virus" pneumonia (300) and "atypical bronchopneumonia" (94). It is like calling a white rose an atypical rose because roses are usually thought of as red. Furthermore, since the pneumonias under discussion have been far more common in recent years than the lobar form, it is a question as to which now should be considered as "typical" (114, 155a). There would be much less confusion in thinking if the viral pneumonias were not habitually compared against lobar pneumonia as the standard, or if they were not so commonly thought of as descending infections (26, 202) or as "complications" (26, 114, 238) of mild diseases of the

respiratory tract. Viral pneumonias comprise an important independent syndrome of which influenza is a closer analogue.

There is, indeed, legitimate objection to the terms viral or virus pneumonia so long as the causative agents are not unequivocally established (135, 155a, 183), yet these terms are widely used. As will be shown presently, however, the evidence favoring the viral etiology, except for the ultimate proof, is almost conclusive. It may be pointed out in this respect that poliomyelitis, yellow fever and smallpox were considered to be viral diseases many years before the causative viruses were isolated. Infectious hepatitis and infectious mononucleosis are at present regarded as viral diseases, yet viruses have not been recovered therefrom. The adjective viral, like bacterial or protozoal, is broad enough to allow for the possible existence of several implicated agents. There is objection, however, even to the designation *pneumonia*, since in many instances the 7 mild nonpneumonic attacks of apparently the same disease are thereby excluded. To encompass all forms of the disease, the term viroid, implying a virus-like infection, has been proposed (245) for temporary use until the various causes are discovered. It has precedent in the words typhoid (typhus-like), varioloid and others.

The appellative dilemma will persist until the cause or causes are discovered and the diseases can be named accordingly, as in the case of influenza A and B. The term influenza covers both mild and pneumonic forms of the entity, and the letters A and B indicate the specific agent. In this review the term viral pneumonia is used for simplicity with realization that it should be replaced by better ones in the future.

Etiology. Before etiologic studies were made, transitory pulmonary shadows as seen (120, 317) in roentgenograms were regarded as complications of mild respiratory disease probably caused by aspiration of exudate (238), atelectasis (114), secondary bacterial invasion (107) or descending infection (26). The opinion that the disease is of viral origin is based on (a) the close analogy with other diseases of known viral origin as regards epidemiologic, clinical, pathologic, and therapeutic characteristics, (b) absence of demonstrable evidence of causal bacteria, and (c) on the results of studies discussed as follows:

Since 1938, vigorous attempts have been made to discover the causative agents, but without decisive results. The problem is complicated (a) by the probable existence of a number of causative agents, filtrable or otherwise, which separately or synergistically may give rise to clinically similar diseases, (b) by the existence of numerous viral pneumonic diseases of experimental animals, (c) by the possibility that both man and animals may harbor these agents, (d) by the similar clinical and pathologic changes evoked by them, (e) by the probable biologic instability of viruses, and (f) by the complexity of the technic involved in studies of viruses and their differentiation.

The first direct attempt to isolate a virus from patients with viral pneumonia was made by Reimann (239, 240) with the aid of Stokes, Kenney, and Shaw (97, 98), and Francis and Magill (155a) in whose laboratories the studies were made. Evidence was obtained of transmission to mice and

causing low-grade pulmonary and meningeal disease, but the virus was lost in transfer. Whether the virus came from the patient or was present in the mice was a dilemma which has pervaded all subsequent work. During extensive studies from 1938 to 1947 about 25 related or unrelated filtrable agents, including those of the psittacosis group as listed on a previous page have been encountered and considered as possible causes, but none save a few of the psittacosis group has been generally accepted as such. The most important studies have been made by 3 groups of workers led respectively by Horsfall, Eaton and Dingle.

List of Agents Associated with Viral Pneumonia

Virus of Stokes et al., Francis and Magill (97, 98)
Mongoose virus (Wier and Horsfall, 103)
Pneumonia virus of mice (PVM, Horsfall and Hahn, 89)
Mouse pneumonia virus (Dochez, 81)
Mouse pneumonia virus (Gordon, Freeman, Clampit, 88)
Guinea pig virus (Rose, Molloy, 96)
The AP or cotton rat virus of Eaton (82)
Virus of Rhoads (246a)
Virus of Johnson (141)
Cat virus (Howard, 77)
Grey lung virus of mice (Andrewes, 76)
Streptococcus MG (Thomas, 101)
Viruses of the Psittacosis group listed on page 173.

The PVM virus of Horsfall: In 1940, a virus of suspected human origin was transmitted to the mongoose (103), but in later studies (80) the results were not duplicated. Horsfall and Hahn (89) then isolated a pneumonia virus from mice (PVM) which seemed to be related to the "mongoose" virus. It also resembled the virus of influenza in size and in the nature of pneumonia it caused in mice, and both had minor antigenic components in common. It was thought to be associated with pneumonia in man because neutralizing antibodies appeared in animals injected with patient's plasma (90). It also was discovered that for unknown reasons convalescent serum from patients when injected into mice inoculated with sputum, prevented the development of antibodies against PVM. Antibodies against PVM occur in a wide variety of experimental animals and in man, suggesting its wide natural distribution (92), if antibodies can be depended upon to indicate previous infection with the virus. In later studies by others (78, 84) similar antibodies could be evoked nonspecifically. Viruses similar to or related to PVM, were recovered from hamsters and cotton rats by Eaton's group (84) and from mice by Dochez's group (81). The latter investigators (95) observed the virus to cause clumping of murine erythrocytes in the manner of chicken red cell agglutination by influenza virus. A suspension of lung tissue from a patient with pneumonia also agglutinated homologous erythrocytes and guinea pig erythrocytes but not those of fowl. A virus isolated by Gordon and his coworkers (88) may also be related to PVM but the final classification of all related strains is not yet possible.

The cotton rat virus of Eaton: A virus different from the other known ones was obtained from cotton rats inoculated intranasally with exudate of patients with pneumonia (82). Belief that this virus may be an important cause of pneumonia was based on the demonstration of the virus in the lung or in the sputum by the transmission of infection to animals (85), by the growth of the virus in chick embryos (86), and by the increase in neutralizing antibodies in the serum during and after an attack (87, 94). A cold agglutinin appeared in the blood of most patients from whom the virus was apparently derived. In Breslow's epidemic (121), serums from some patients with mild, non-pneumonic attacks as well as those with pneumonic forms neutralized the virus. In further studies (87a) the agent was named AP (atypical pneumonia) virus. Significant increases in antibody titer against AP virus were demonstrated in 62 per cent of 84 cases of viral pneumonia and in 19 per cent of 77 cases of similar but mild nonpneumonic disease of the respiratory tract.

Eaton estimated that about 60 per cent of viral pneumonias may be caused by the "cotton rat" virus, less than 10 per cent by the viruses of influenza, the psittacosis group and other known viruses, and the remainder by causes unknown.

Streptococcus MG (344): Another group of investigators (78, 79, 91, 99, 101) was not impressed with the importance of the virus obtained from cotton rats as a cause of pneumonia in man, since it, or one like it, often exists naturally in cotton rats and other rodents. Neither could it be transmitted in further passage. Instead they assign etiologic significance to an indifferent streptococcus called MG or 344. Others have incriminated green-producingstreptococci as a cause of pneumonia or as increasing the severity of a viral pneumonia (264a) or as often present (120, 227, 238, 291). Streptococcus MG is apparently of a single type related immunologically to Streptococcus salivarius type 1. A specific polysaccharide endows it with type specificity. It is found in the throat of about 12 per cent of normal persons, in 25 per cent of those with other diseases of the respiratory tract, in 55 per cent of the patients with viral pneumonia studied by the authors, and in the lung tissue in 75 per cent of fatal cases. Specific agglutinin, precipitin for the polysaccharide, and swelling of the capsule occurs in the serum of patients. The polysaccharide when injected intradermally causes a reaction in certain patients, particularly in severe attacks. The specific agglutinin is not related to the cold agglutinin which often develops in the same patients, nor with other concurrent serologic peculiarities.

At least 4 peculiar immunologic reactions occur in the serum of certain patients convalescent from viral pneumonia: (a) cold hemagglutination, (b) fixation of complement by a variety of dissimilar agents, (c) prevention of formation of antibodies to PVM by convalescent serum, and (d) agglutination of indifferent streptococci. The reactions are usually strongest in severe attacks.

Several possible relationships of streptococcus MG to the disease are as follows: (a) the serologic reaction may be of the same order as the Weil-Felix reaction which involves similar antigens of dissimilar microorganisms (100), (b) streptococcus MG and other indifferent streptococci may be secondary

invaders (99, 291) and (c) the streptococci may be primarily involved in the cause of pneumonia either alone or synergistically with a filtrable virus as a complex infection analogous with that of swine influenza (91, 101).

Finland and his associates (291) corroborate the frequent presence of agglutinin for streptococcus MG in the acute phase of pneumonia in significantly greater proportion than in normal persons or during other disease. A titer rising to 1:40 or more was limited mostly to viral pneumonias. Similar agglutination was noted with a strain of streptococcus called E. S. which could not be related etiologically to the disease. Almost all of the patients with viral pneumonia who had agglutinin for the streptococci also had cold agglutinin in significant titer (290, 291, 292). There was some correlation between the presence of agglutinin in maximum titer for both strains of streptococci and the maximum titer of cold agglutinin. The agglutinins are distinct from each other suggesting that there is an antigen in these streptococci which is in some way related to the etiologic agent of viral pneumonia (290). Perhaps the streptococcus coexists as a non-pathogen and becomes antigenic during pneumonia.

Comment: The suggested synergistic relation of streptococcus MG and a virus to pneumonia as "complex infection" would be the first known example of its kind in man. The problem brings to mind the polemic about Bacterium pneumosintes, the bacillus of Pfeiffer (H. influenzae) and its prolonged erroneous connection with influenza, and the similar circumstances of the socalled hog-cholera bacillus in relation to hog cholera. These bacilli were often present in the respective diseases but none is the cause. Most necropsy studies on patients dying from viral pneumonia have revealed pneumonic lesions with few or with no demonstrable bacteria of any kind (164, 291). Streptococcus MG is said to be sensitive to penicillin (101) yet penicillin has no therapeutic influence in viral pneumonias except perhaps for some caused by the psittacosis group of agents. Lastly, and as discussed in the next section, disease identical with viral pneumonia was induced in volunteers with filtered, bacteria-free secretions from patients. Agglutinin for streptococcus MG developed in only 2 of 10 subjects in titer of 1:32. The streptococcus was present in the throat of one-third of the men before the experiment and in one-half of them afterward whether pneumonia developed or not. In these experiments streptococcus MG apparently played no etiologic role, nor did 26 other unrelated strains of indifferent streptococci isolated from the volunteers (75), unless it is postulated that the virus provoked the resident streptococci into antigenicity or invasive activity. No attempts have been made to induce disease with streptococcus MG in volunteers (135).

Transmission experiments: The experience of the Commission on Acute Respiratory Disease of the U. S. Army (75) has not supported the etiologic connection with viral pneumonia of any of the agents so far discussed. In the disease studied no agents of the psittacosis group nor evidence of their presence were encountered. After the unsuccessful attempts of others (102), members of the Commission made 3 successive experiments on groups of volunteers by causing them to inhale unfiltered, filtered and autoclaved nasopharyngeal washings from patients with viral pneumonia. The results of the same studies are published in several places. Of 60 volunteers who inhaled filtered or unfiltered washings, 47

of 75 per cent developed some form of illness, the beginning most often in the 3rd days later. Of the 47, 18 or 38 per cent developed bronchopneumonia, with the rest mild illness of the respiratory tract. The bronchial period of the mild bronchopneumonia usually a few days and most of the pneumonias usually more than 5 days. It was likely, but unproved, that the mild forms and the pneumonias were caused by the same agent. Surprisingly, pneumonia developed in several volunteers who had had undergone wastings suggesting the stimulation of a latent virus in human tissues. But for these disturbing incidents, the experiments thus far provide no best evidence that a filterable agent is the cause of viral pneumonia. In one of the 3 experiments, mild respiratory illness took place in the serum of 5 of 11 volunteers with pneumonia, and in 2 of 11 with mild illness, but experiments for complications had occurred in only 2. No significant changes occurred in the bronchial flora of the nasopharynx before, during or after pneumonia or mild illness developed. The latter observations are noted by others, but in contrast with previously reported studies in which one bacterium was secured in large or increase in the number and variety of potentially pathogenic bacteria [illegible].

Other viruses. A number of other viruses were encountered by various investigators. One virus pneumonia in guinea pigs [illegible] was apparently derived from guinea pig lungs in another field, caused pneumonia, delayed from guinea pigs and in another field caused pneumonia. It was more severe pneumonia if accompanied by nonhemolytic streptococci. A virus was isolated from the lungs of one white developed pneumonia while = persons in the same household had similar illness [illegible]. The virus could not be transferred to mice and it is uncertain if the same virus caused pneumonia in persons and in mice [illegible]. A transmissible agent called the pig lung virus was isolated from mice by Andrewes and Glover [illegible].

Comment. It is obvious that most investigations suggest a virus as several viruses being able to be associated with acute respiratory illness as the causes of viral pneumonia, but the results reported in the field of this section and from the results that are contained in studies on mechanisms can be drawn in present. This review is therefore in the nature of a report of progress.

Incidence. It is not possible to estimate with accuracy the general incidence of the viral pneumonias except by inferences based on studies of small well-controlled groups. Even then, the issue is confused by uncertainties in diagnosis, by the selection of different studies and by the fact that the pneumonic forms of certain studies represent only the serious forms of illness, pneumonia, pleurisy, etc. and of the diseases under discussion which are not reported in official health statistics [illegible]. Furthermore, various observers unfortunately include only those with clinical or roentgenologic evidence [illegible] of pneumonia in their series and exclude or report separately those with only minor or mild respiratory illness or pneumonia [illegible].

The incidence of viral pneumonias and of the infections just mentioned varies greatly from year to year as do other respiratory diseases. The distribution of these is likely to be uneven, some being an epidemic period, some communities may be severely affected and others not at all.

It is doubtful if the viral pneumonias are usually transmissible in epidemics. It is

more likely that the past few years have encompassed the crest of a wave-like epidemic recurrence (142) together with awareness of the disease after its delineation in 1938, general clinical interest in it, greater interest in etiologic diagnosis, and the increasing use of diagnostic roentgenography. According to Francis (155a), viral pneumonia might represent the underlying process of most bacterial pneumonias, and is now more noticeable, or unmasked, so to speak, since the natural and induced decline of the numbers of bacterial pneumonias. Military mobilization and other disturbances of the population may have increased the incidence after 1941. Some idea of the waxing and apparent waning of interest in the viral pneumonias is indicated by the dates of publication of pertinent papers included in this review. Between 1937 and 1947 the number of papers published in the respective years is about as follows: 5, 9, 6, 9, 32, 74, 74, 45 and 22. A large proportion of the publications between 1943 and 1945 came from physicians of the armed forces.

There is no doubt, however, that the proportion of recognized viral pneumonias to lobar pneumonia has changed recently due to the reduction in numbers of the bacterial forms by therapy with sulfonamide compounds and penicillin and to the factors mentioned in the preceding paragraph. In 1941, for example, viral pneumonias comprised 15 per cent of all pneumonias in one hospital (242) and in 1942 they outnumbered the pneumococcal pneumonias by 3 to 1. Viral pneumonias outnumbered all other forms of pneumonia in the armed forces during the war years (140, 183, 197). In 1947, pneumococcal pneumonias again exceeded the viral forms in number.

Several studies among relatively "closed" groups of persons gave some idea as to the local prevalence of the disease. In one hospital group (241) of 800 persons, over a period of 2 months, 400 persons had acute disease of the respiratory tract. Of the 400, 75 per cent with "colds" remained ambulatory, 25 per cent were sick enough to go to bed, 12 per cent had recognizable tracheobronchitis and half of these or 6 per cent had pneumonia. In Favour's (151) group of 300 persons exposed to infection 231, or 70 per cent contracted disease; that is 12 per cent had pneumonia, 16 per cent mild disease and 71 per cent had tracheobronchitis. Daniels (138) reported pneumonia in 15 per cent of 90 students during a 2 month period. In Robertson's experience (249) with 450 students, 77 or 17 per cent were sick; of the 77, 70 per cent had mild disease and 30 per cent had pneumonia. Numerous other observers recorded a similar distribution of cases (118, 120, 121, 174, 186). In the aforementioned (75) small group of 60 volunteers experimentally infected with large inoculums, the incidence was much greater; 78 per cent developed disease; that is, 29 had mild symptoms and 18 had pneumonia. In an army post, the proportion of mild to pneumonic cases was rather constantly as 10 is to 1 (141,197). There was a much greater incidence of disease in new recruits as compared with seasoned soldiers (197). Important evidence of the prevalence of unsuspected pneumonia during mild respiratory disease has emerged from routine mass roentgenography of ambulatory patients (109, 118, 120, 156, 238). Ramsay and Scadding (238) report transitory pulmonary shadows in 1.7 per cent of 1220 persons with colds. According to recent compilation

(246), evidence of pneumonia was reported as being present in 12 per cent of "colds", 12 per cent of cases of pharyngitis, 15 per cent of "febrile catarrh", 6 per cent of "viroid" and in 14 per cent of patients with influenza.

Statistics of larger groups as at Camp Claiborne show an average incidence viral pneumonia as 88 per 1000 per week during a summer epidemic and 28 per 1000 per week in the following winter months (141d). The incidence in the Army in general was about 25 per cent of all respiratory tract disease and 75 per cent of all pneumonias (141d). In the Navy, the incidence was 2.79 per 1000.

Viral pneumonias in epidemic form were observed on all continents among native populations (115, 120, 170, 173, 221, 230, 261, 306, 315) and especially in American Armed Forces (120, 233, 271). They occur in tropical climates (110a, 123, 176, 174, 177, 198, 223, 269, 274).

Seasonal incidence: Most of the recorded epidemics occurred in the cold months and sporadic attacks occur throughout the year (117, 138, 141, 160, 201, 220, 229, 241, 262). Epidemics also occurred in the summer months (124, 141, 145, 201, 217, 248, 284) and in the late fall (124, 151, 193, 204). The incidence of pneumonia closely parallels that of minor respiratory diseases (26, 155a, 141, 197, 160, 210, 241), but exceptions occur (117, 138, 194, 239, 274) when only pneumonic forms are present. Severe sporadic cases closely resembling those caused by agents of the psittacosis group occur at any season (17, 201, 220, 239, 242).

Age and sex: The majority of reports deal with pneumonias as they occur among young adults in schools and in the armed forces, but all ages from infancy to old age may be affected (117, 194, 290). There is no predilection for either sex except in the incident reported by Kotin (194) in which the disease occurred only in genetically related female members of a family, in this instance suggesting genetic susceptibility.

Epidemiology. The probable existence of several entities of viral pneumonia permits discussion of its epidemiology only in general terms. The disease seems to occur in two forms, one consisting of severe, isolated, nonseasonal sporadic cases; the other, far more common, in epidemic form probably consisting of disease characterized by mild respiratory tract infection commonly called colds, grip, viroid, pharyngitis and influenza and their accompanying severer pneumonic forms (243).

Toward all of these diseases, people individually or as large groups, have varying degrees of resistance, immunity or susceptibility which vary at different times probably as the result of previous infection and from other unknown causes. Epidemics therefore involve varying proportions of a population (131, 141, 276, 284). At times viral pneumonia seems to be highly communicable (151, 284) and at others not (141, 144, 145, 161, 193, 201, 239, 274). In one family group five female members contracted severe pneumonia from a sixth, yet no other disease of any kind occurred in other male family members or contacts nor in the community (194). Other outbreaks also seem to consist of severe forms alone (94, 138, 239) but it must be pointed out that many observers reject mild nonpneumonic forms as being unrelated. Severe sporadic cases are often

caused by the viruses of the psittacosis group (17, 63, 242) but in other instances they are not, and no evidence of contact with known sources in birds or man can be discovered (242, 274). Persons with mild infection may transmit disease which is severe in others, and the opposite may occur (201). The occurrence of pneumonia as an episode in the course of a basic disease is determined by factors other than the causative agent itself (155a). Controlled experiments to see if exudates from patients with the mildest forms of disease give rise to pneumonic forms in volunteers are awaited. The disease usually seems to be more contagious than pneumococcal pneumonia and less so than measles, for example. Among large groups, outbreaks are "spotty", affecting some subgroups and not others (141, 161). In Young and Storey's (284) experience in a school, 27 per cent of one class of students were affected, and only 5 per cent of another. During the same outbreak 9 per cent of the whole group of 402 persons in the institution had mild disease of the respiratory tract.

From many clinical observations of apparent person to person contagion (141, 142, 151, 161, 162, 193, 194, 201, 206, 210, 241, 262), from the experimental transmission of the disease to volunteers (75), and from carefully studied epidemics (204, 276, 284), all evidence suggests the communicable nature of viral pneumonias. Undiagnosed patients, persons with inapparent infections and probably healthy carriers (141, 242) may spread infection. It is transmitted by the airborne route by expelled secretions, but other means of transfer by soiled dishes or clothing have not been excluded (274).

Epidemics may be explosive covering a period of several weeks (121, 161, 186, 241, 284) or spread over several months in more or less continuous, recurrent (141, 151) or sporadic form (274).

Immunity: Little is known of immunity because of incomplete etiologic information. Some degree of specific immunity can be postulated by analogy with other infections. Gallagher (161) did not observe second attacks in any case, but Dochez (142) noted 4 relapses in one case, and Berryhill (117) records 7 patients who had recurrences within 2 years. One of the volunteers infected in the transmission experiments had had a previous attack (75). Favour (151) records examples of multiple attacks. It is of course impossible to tell whether subsequent attacks are caused by the same agent or by different ones against which immunity is not expected.

Pathology. Since the mortality rate is low, only about 20 necropsy reports are available and of these many are incomplete. With the attention of clinicians and pathologists focussed chiefly on the lungs there are, unfortunately, no descriptions of the pathologic changes in the upper air passages including the trachea. Gross changes in these regions seen clinically are described on a later page.

Lungs and bronchi: Since the tissues of the lung have a limited capacity to react to infections and to injury by diverse agents, the lesions observed in the fatal cases of pneumonia of unknown origin are nonspecific and cannot be distinguished from those caused by various viruses, certain bacteria, roentgen rays

or toxins (71, 267) except for the presence of inclusion bodies in certain instances (105, 166, 185, 232).

Grossly an affected lung is heavy. The pleural surface may show patches of fibrinous exudato but effusion is uncommon. On section the pneumonic areas vary greatly in size and distribution. They are patchy and often in different stages of evolution. Areas of atelectasis and emphysema are often found. The regional lymph nodes may be slightly enlarged.

Histologically the picture is essentially that of an interstitial pneumonitis. There is acute focal bronchiolitis and desquamation of the mucosa. Ulceration may be extensive (141). The lumens contain purulent or mucoid exudate containing degenerated epithelial cells, mononuclear cells, a few polymorphonuclear leukocytes, and a few bacteria of varous kinds (201). The walls of the larger bronchi are intensely inflamed and are infiltrated with mononuclear cells and a few polymorphonuclear ones, but no bacteria are seen. The lumens often contain a tenacious exudate. Sloughing and erosion occur (254). There is often squamous metaplasia of the epithelium (94, 201). The bronchioles are often dilated and their walls are infiltrated chiefly with mononuclear cells which also invade the adjacent peribronchial tissue, the alveolar walls and the pulmonary septums. The alveoli may be airless and often contain an exudate of mononuclear cells and a few polymorphonuclear cells but not much fibrin. No inclusion bodies nor elementary bodies can be seen. Bacteria rarely can be seen or cultivated from the lesions. When secondary bacterial invasion occurs, the lesions are modified and resemble those caused by the respective varieties of bacteria or of mixtures thereof. Abscesses may develop. There may be acute, follicular splenitis and the mesenteric lymph nodes may be swollen (141c, appdx. J.). More detailed description can be found in the reports of cases (94, 120, 124, 141c [appdx. J.], 164, 193, 201, 202, 208, 222, 223, 231, 242, 246a, 250, 251, 254, 314, 320).

Cerebral changes: Clinical evidence of encephalitis agrees with the occasional presence of lesions in the central nervous system. Some changes seem to be caused by the causative agent of the pneumonia and others resemble the "toxic encephalopathy" common to many infectious diseases. From analogy with other infections there is reason to believe that the agent of pneumonia may also be neurotropic. Perrone and Wright (231) describe cerebral hemorrhages, perivascular cuffs of monocytes and astrocytic and glial proliferation. Golden (164) found similar lesions. Encephalitis and meningitis are recorded by Campbell (124). Two cases of encephalitis with perivascular hemorrhages throughout the brain occurred at an army post (75c). Ingleby (185) described vascular thrombosis, acute degeneration of the nerve cells but no perivascular exudate in 2 cases. Inclusion bodies were found in all parts of the brain, in the nerve cells, and in the perivascular areas. Similar inclusions, resembling those described by Adams (105), were found in the bronchial epithelium where the exudate, like the pulmonary infiltrate, was composed chiefly of mononuclear cells.

Clinical. Predisposing factors: As in other acute infections of the respiratory

tract, chilling (141d), overwork (151), fatigue, and malnutrition seem at times to be predisposing factors. Antityphoid vaccination seemed to play a role in a few cases (227) and in one group, pneumonia occurred more often in persons with malaria than in others (110a). In many cases no predisposing factors are obvious (145).

Incubation period: Clinical observations in one study in which the mild nonpneumonic and severe pneumonic forms were considered as one disease suggested that the incubation period may be as short as one or two days (241). A similarly short period was measured in the transmission experiments (75) in persons contracting mild disease, but it lasted more than 5 days in those who developed pneumonia. It was usually 10 to 14 days. The longer incubation period varying from 5 (188) to 26 days (167) has been almost universally reported in instances where it could be reasonably accurately dated (117, 141d, 138, 151, 161, 193, 201, 220, 262, 276). The usual period seems to last from 17 to 19 days (255).

Onset: Considerable confusion exists in describing the onset depending upon whether it is dated from the appearance of the first symptoms of mild disease or from the first evidence of pneumonia. Many observers, probably erroneously, regard the earliest symptoms as "prodromal" ones or as those of an etiologically different disease which predisposes to pneumonia as a "complication". Several reports record immediately "preceding" mild respiratory tract disease in 25 to 40 per cent of patients which in all probability is the early period of the disease itself. As noted in the accompanying table there is divergence also in describing the manner of onset. Several authors regard it as usually abrupt. The first awareness of being sick may indeed be abrupt but the onset is rarely, if ever, as violent as in lobar pneumococcal pneumonia. The majority of clinicians record the onset usually as being gradual; that is, the patient feels as though he has "caught a cold" which over several days becomes worse until pneumonia is discovered.

Clinical Forms. As stated previously the mild forms of disease during an outbreak of viral pneumonia cannot be distinguished etiologically from the more severe ones but can only be proved to be due to the same cause after the agent or agents are discovered. Yet the following evidence favors the view that they are etiologically the same: (a) the concurrence of mild and severe forms during epidemics; (b) the transmission experiments wherein both mild and severe forms were induced and cold agglutinins developed in most cases of both forms (75); (c) the presence of neutralizing bodies for the "cotton rat" virus in mild and severe forms in epidemics (87a, 121); (d) the accidental finding of pneumonia during mass roentgenography in ambulatory persons (109, 118, 120, 317); (e) the similarity of the symptoms of the mild and severe forms (75, 121, 141, 186, 241), and (f) the analogy with diseases of known origin such as influenza.

If subsequent studies confirm the etiologic unity of the mild and pneumonic forms of the disease, it may be said that the majority of attacks do not advance beyond the mild stage. The proportion of mild to severe cases in reported outbreaks is remarkably similar and is given in approximate percentage as follows:

AUTHOR	NO. OF CASES	MILD NONPNEUMONIC	MODERATELY SEVERE	SEVERE
Reimann, Havens (241)	400	75	19	6
Robertson (249)	77	70		30
Commission (75)	47	70		30
Breslow (121)	191	59	24	16
Iverson (186)	70±	50	40	10
Favour (151)	231	16	71	12

Inapparent infection: Cold agglutination appears and disappears in some pesons without any other evidence of disease (287). If the cold hemagglutinin test is reliable as diagnostic evidence, the infection apparently occurs in certain persons who manifest no clinical evidence of disease (75e, 287).

Mild forms: The mildest forms of infection in the majority of cases in some outbreaks are described by several authors (121, 141, 151, 186, 239, 241, 249) as being clinically indistinguishable from other commonly occurring "colds" (246). Those occurring in the transmission experiments were similar (75c). The patients may become suddenly or gradually aware of discomfort. There is nasal congestion, slight sore throat, lymphoid hyperplasia, cervical adenopathy, headache, malaise, anorexia, irritation of the conjunctiva, weakness, irritability, pain in the eyeballs and unproductive cough. There may be a feeling of coldness or shivering, but there is rarely any fever or rhinorrhea. Rales may be heard (75e). Roentgenograms usually show normal pulmonary shadows but in occasional cases, one is surprised to find transient densities of either tracheobronchitis or of pneumonia. Persons almost always continue with their regular duties, medicate themselves and rarely consult a physician unless obliged to by institutional rules. They serve as migratory disseminators of infection. The discomfort lasts a day or two, disappears, relapses one or more times or progresses to a more severe stage or directly into clinical pneumonia. In general, but with striking exceptions, the severity of attacks is in proportion to the extent and intensity of the inflammation of the mucous membranes. Any part of the respiratory tract may be involved independently, in succession, or simultaneously.

Moderately severe nonpneumonic forms: The severer forms may begin as such or evolve from the mild ones. The symptoms are similar except for greater severity. The discomfort is usually great enough to oblige rest in bed. Chilliness is more common, aching more severe and the cough tends to be paroxysmal and unproductive. Photophobia, sweating, hoarseness and aphonia occur. Fever of low or high irregular type is the rule. There is seldom much exudate. Some patients with intensely inflamed throats have surprisingly little pain therefrom. Pain in the chest or abdomen results from severe coughing, and nausea, vomiting and diarrhea may occur (121, 151, 186, 241). The course lasts several days to a week or more. Relapses may occur (151), or the symptoms may increase as pneumonia develops.

Patients look sick with flushed skin and reddened conjunctivas. The mucous

membranes of the upper part of the respiratory tract are inflamed and dry. Congestion and edema are often great enough to obstruct the nares. The lymphoid follicles and tissue of various parts of the tract from the nares to the trachea are intensely red and dry with varying degrees of involvement. Pin point areas of crusting and excoriation or resembling hemorrhages are present on the inflamed nasal septum. Inflammation of the larynx is due partly to the infection itself and partly to coughing. Cervical adenopathy is occasionally present. A few rales may be audible in the parasternal and interscapular areas. Roentgenologically there was evidence of tracheobronchitis with increased density of the bronchial markings in 23 of 86 cases in one series (318).

Pneumonic forms: Attention should again be drawn to the likelihood that the syndrome of viral pneumonia is composed of a number of etiologic entities all of which seem to be characterized by inflammation of the mucous membrane of the nose, pharynx, larynx, trachea, bronchi, bronchioles and lungs, each of which may be involved independently or in various combinations at once or in succession, with varying degrees of severity of constitutional symptoms (26). Since most observers have devoted their entire attention to the pneumonic forms which are usually the most severe, the majority of reports deal with them. So many adequate reviews (117, 140, 144, 255) and descriptions of the clinical aspects of this form of pneumonia have been published (79, 94, 104, 131, 161, 202, 204, 227, 229, 239, 241, 276), that no greatly detailed account is needed here.

The clinical characteristics of the pneumonic forms may be summarized in a short paragraph (91) which in all essentials is the same as the first description given in 1938 (239), as follows: a gradual and often ill-defined onset, a remittent fever which is seldom very high, a pulse rate often relatively slow, a normal or slightly increased respiration rate, slight indefinite or absent physical signs of pneumonia which are strikingly at variance with roentgenographic evidence of pulmonary invasion, a cough which is often nonproductive but paroxysmal, a normal or slightly abnormal leukocyte count, recovery by lysis and few complications.

A statistical compilation of the main features of 2500 cases as described by 13 observers is given in table 1. On the whole, the figures are remarkably similar except for certain divergences as, for examples, in the matter of onset and the incidence of headache or sweating. Recorded differences may be accounted for by the probable observance of different entities and by differences of opinion, point of view, interest and interpretation by the observers. In many instances striking features noted by some are not mentioned by others. Differences may also arise by the statistical exclusion of cases without roentgenographic evidence of pneumonia (79).

Onset: The onset is stated to be gradual in most reports, commencing as an ordinary mild infection of the respiratory tract, but becoming worse over 3 or 4 days, in the manner of the milder forms just described. Several authors report an abrupt onset (104, 133, 169, 209, 220), sometimes without nasopharyngitis (271) but rarely if ever is it as violent as that of pneumococcal lobar pneumonia.

Symptoms: Patients usually feel as if they are developing a cold with lassitude, fatigue and weakness, but the symptoms increase in intensity for several days

and new ones appear. As shown in the table, cough, fever, malaise, headache, general aching, chills, slight sore throat and discomfort in the chest are the most common complaints. The cough is the most common and often the most distressing feature. It is paroxysmal and is often precipitated by sudden changes of position. It aggravates headache, sore throat, pain in the chest and abdomen, insomnia and exhaustion. It is unproductive or productive of only slight amounts of mucoid or mucopurulent sputum in the early period and resists most forms of treatment. Later in the course mucopurulent sputum seldom exceeding 30 cc. a day may be raised. It is occasionally bloodstreaked, rarely bloody or rusty (79, 144). In rare cases there may be neither cough nor sputum (117, 237, 242, 274).

Fever rises gradually and may never exceed 38.4 C (101 F) or may reach 40.5 C (105 F). It usually rests between 37.8 C (100 F) and 39 C (102 F) and follows no regular pattern. It is usually moderately remittent, less often persistently high or intermittent, and falls by lysis, rarely by crisis (79, 141, 204). In rare instances the fever may be diphasic (104, 180, 202, 239, 255). Discomfort is often in proportion to the fever but exceptions occur. Some patients with high fever do not appear to be very sick (109, 141, 156, 161, 168, 227, 274). Some patients may be afebrile throughout the course (141, 144, 177, 204). Chilliness, chills or feverishness often occur and may or may not be accompanied by sweating which at times is drenching (117, 214, 239, 255, 217). Sweating may persist during convalescence (117). Rigor rarely occurs. Anorexia, malaise and aching are commonly noted but the severe prostration common to influenza is infrequent. Headache and/or drowsiness is of particular interest since it is often severe enough to suggest encephalitis. Encephalitis may occur (104, 110, 152, 168, 169, 179, 239). Pain in or behind the eyeballs, especially on ocular movement, conjunctival irritation and photophobia occur (79, 141, 144, 204, 212, 239).

Pharyngeal reddening occurs in most patients but there is seldom more than slight soreness and dryness which is aggravated by cough (79, 168, 241). Coryza is not striking (237, 241, 220). Nasal obstruction occurs. Hoarseness and aphonia are not often recorded (204, 208, 239). Discomfort, pain and burning in the substernal area may be caused by the inflammation itself or by coughing. Pain along the costal margins, in the upper or lower part of the abdomen is often caused by muscle soreness from coughing (124, 227, 241). Abdominal pain has led to unnecessary appendectomy (168, 227). Pain from pleuritis with friction occasionally occurs in some series (79, 104, 144, 177, 201, 208, 229, 239) and not in others (171).

The pulse rate often, but not always, is slow in proportion to the fever. If slow at first it may increase later in the disease. Curiously, it is often faster in mild than in severe forms and may indicate the degree of "toxemia" (241). In certain reports it never exceeded 100 in 70 per cent of cases (229). Relative bradycardia and high fever often suggest psittacosis or typhoid fever (239).

The respiratory rate is seldom increased in proportion to the extent of the pneumonia. Dyspnea and cyanosis are more often in proportion (167, 241).

Mental confusion, dizziness, delirium, somnolence, stiff neck and abnormal

membranes of the upper part of the respiratory tract are inflamed and dry. Congestion and edema are often great enough to obstruct the nares. The lymphoid follicles and tissue of various parts of the tract from the nares to the trachea are intensely red and dry with varying degrees of involvement. Pin point areas of crusting and excoriation or resembling hemorrhages are present on the inflamed nasal septum. Inflammation of the larynx is due partly to the infection itself and partly to coughing. Cervical adenopathy is occasionally present. A few rales may be audible in the parasternal and interscapular areas. Roentgenologically there was evidence of tracheobronchitis with increased density of the bronchial markings in 23 of 86 cases in one series (318).

Pneumonic forms: Attention should again be drawn to the likelihood that the syndrome of viral pneumonia is composed of a number of etiologic entities all of which seem to be characterized by inflammation of the mucous membrane of the nose, pharynx, larynx, trachea, bronchi, bronchioles and lungs, each of which may be involved independently or in various combinations at once or in succession, with varying degrees of severity of constitutional symptoms (26). Since most observers have devoted their entire attention to the pneumonic forms which are usually the most severe, the majority of reports deal with them. So many adequate reviews (117, 140, 144, 255) and descriptions of the clinical aspects of this form of pneumonia have been published (79, 94, 104, 131, 161, 202, 204, 227, 229, 239, 241, 276), that no greatly detailed account is needed here.

The clinical characteristics of the pneumonic forms may be summarized in a short paragraph (91) which in all essentials is the same as the first description given in 1938 (239), as follows: a gradual and often ill-defined onset, a remittent fever which is seldom very high, a pulse rate often relatively slow, a normal or slightly increased respiration rate, slight indefinite or absent physical signs of pneumonia which are strikingly at variance with roentgenographic evidence of pulmonary invasion, a cough which is often nonproductive but paroxysmal, a normal or slightly abnormal leukocyte count, recovery by lysis and few complications.

A statistical compilation of the main features of 2500 cases as described by 13 observers is given in table 1. On the whole, the figures are remarkably similar except for certain divergences as, for examples, in the matter of onset and the incidence of headache or sweating. Recorded differences may be accounted for by the probable observance of different entities and by differences of opinion, point of view, interest and interpretation by the observers. In many instances striking features noted by some are not mentioned by others. Differences may also arise by the statistical exclusion of cases without roentgenographic evidence of pneumonia (79).

Onset: The onset is stated to be gradual in most reports, commencing as an ordinary mild infection of the respiratory tract, but becoming worse over 3 or 4 days, in the manner of the milder forms just described. Several authors report an abrupt onset (104, 133, 169, 209, 220), sometimes without nasopharyngitis (271) but rarely if ever is it as violent as that of pneumococcal lobar pneumonia.

Symptoms: Patients usually feel as if they are developing a cold with lassitude, fatigue and weakness, but the symptoms increase in intensity for several days

and new ones appear. As shown in the table, cough, fever, malaise, headache, general aching, chills, slight sore throat and discomfort in the chest are the most common complaints. The cough is the most common and often the most distressing feature. It is paroxysmal and is often precipitated by sudden changes of position. It aggravates headache, sore throat, pain in the chest and abdomen, insomnia and exhaustion. It is unproductive or productive of only slight amounts of mucoid or mucopurulent sputum in the early period and resists most forms of treatment. Later in the course mucopurulent sputum seldom exceeding 30 cc. a day may be raised. It is occasionally bloodstreaked, rarely bloody or rusty (79, 144). In rare cases there may be neither cough nor sputum (117, 237, 242, 274).

Fever rises gradually and may never exceed 38.4 C (101 F) or may reach 40.5 C (105 F). It usually rests between 37.8 C (100 F) and 39 C (102 F) and follows no regular pattern. It is usually moderately remittent, less often persistently high or intermittent, and falls by lysis, rarely by crisis (79, 141, 204). In rare instances the fever may be diphasic (104, 180, 202, 239, 255). Discomfort is often in proportion to the fever but exceptions occur. Some patients with high fever do not appear to be very sick (109, 141, 156, 161, 168, 227, 274). Some patients may be afebrile throughout the course (141, 144, 177, 204). Chilliness, chills or feverishness often occur and may or may not be accompanied by sweating which at times is drenching (117, 214, 239, 255, 217). Sweating may persist during convalescence (117). Rigor rarely occurs. Anorexia, malaise and aching are commonly noted but the severe prostration common to influenza is infrequent. Headache and/or drowsiness is of particular interest since it is often severe enough to suggest encephalitis. Encephalitis may occur (104, 110, 152, 168, 169, 179, 239). Pain in or behind the eyeballs, especially on ocular movement, conjunctival irritation and photophobia occur (79, 141, 144, 204, 212, 239).

Pharyngeal reddening occurs in most patients but there is seldom more than slight soreness and dryness which is aggravated by cough (79, 168, 241). Coryza is not striking (237, 241, 220). Nasal obstruction occurs. Hoarseness and aphonia are not often recorded (204, 208, 239). Discomfort, pain and burning in the substernal area may be caused by the inflammation itself or by coughing. Pain along the costal margins, in the upper or lower part of the abdomen is often caused by muscle soreness from coughing (124, 227, 241). Abdominal pain has led to unnecessary appendectomy (168, 227). Pain from pleuritis with friction occasionally occurs in some series (79, 104, 144, 177, 201, 208, 229, 239) and not in others (171).

The pulse rate often, but not always, is slow in proportion to the fever. If slow at first it may increase later in the disease. Curiously, it is often faster in mild than in severe forms and may indicate the degree of "toxemia" (241). In certain reports it never exceeded 100 in 70 per cent of cases (229). Relative bradycardia and high fever often suggest psittacosis or typhoid fever (239).

The respiratory rate is seldom increased in proportion to the extent of the pneumonia. Dyspnea and cyanosis are more often in proportion (167, 241).

Mental confusion, dizziness, delirium, somnolence, stiff neck and abnormal

TABLE 1

	AUTHORS												
	GALLAGHER (161)	LYGHT (204)	GREEN (168)	CAMPBELL (124)	YOUNG (234)	VAN RAVENSWAAY (276)	COMMISSION (141)	KARPEL (189)	CURNEN (79)	ADAMS (104)	HAMBURGER (177)	PAINTON (229)	MCCOY (208)
	1941	1941	1942	1943	1943	1944	1944	1945	1945	1946	1946	1946	1946
No. cases	52	300	80	200	40	297	69	500	106	50	70	321	420
Onset gradual				63	Most	67	26	26	73	30		70	
Cough	80	80	88	51	100	86	99	69	98	94	79	66	95
Malaise	90					70	77		61	100		33	34
Anorexia									35	100		6	5
Headache	70	55	47		80	48	78		65	100	68	20	25
Aching		60	42	25	80				28	30	33		23
Chills	14	50	48		50	68	75	44	59	74		30	42
Rigor					9	11	13	3			24		
Sweating										56			1
Coryza		30			20	49	41					60	3
Sore throat		30	20	26	70	47	36		30			25	25
Epistaxis	0								15	6			1
Sputum	50					74	81	44	82	88	17	20	
Bloody sputum		4	14	6		26	10		25	28	4	3	
Chest pain	10	38	35	44	50	69	40	20	39	46	37	25	24
Dyspnea		5	9	3	30	21			5	8			0.5
Dizziness		0.6								22		3	1
Nausea	4	10	27				Occ.		28			5	
Vomiting							Occ.		24			5	5
Duration Fever in days	2–18			Less than 6 in 75%			7 in 63%	4 in 60%	0–41, average 10	1–16, average 6		1–9 in 84%	6 in 70%

Average duration of disease days.....	7		5.4							8.6			15–21
Days in Hospital.....			16.4	16 in 69%			Up to 40 in 68%	4–30 in 86%	10 to 73, average 33	14			Up to 35 in 82%
Fever			73		55	97	81		95	100	86	90	63
Pharyngitis.....			65				61		69			60	
Conjunctivitis							20						
Rales.....	60		92			56	93	54	93	96	39	60	81
Dulness.....	60		58			23	41	25	54	22	6	20	28
Friction.....									7	12	6	6	3
Cyanosis.....			11	2		3							
Lymphadenitis.....			5		Several				24	60+			
Pleural fluid					0.5	6			1				
Meningeal signs.....						0.4			6	2			
Complications.....		27				37		3	Rare				

reflexive reactions occasionally occur in the severest form and suggest encephalitis (179, 239). They may develop during defervescence (168). Gastrointestinal disturbances as noted in the table are uncommon, but they are reported by some (79, 121, 168) as occurring in 25 per cent of cases. They are seldom conspicuous. An erythematous eruption may appear early in the course of the disease (179, 193, 235).

Severe forms without pneumonia: Several authors have observed patients with disease identical with severe viral pneumonia except for the absence of clinical and/or roentgenographic evidence of pneumonia either during epidemics (117, 125, 186, 200, 254) or sporadically (244). In one of Iverson's (186) patients the disease lasted 17 days. While the disease cannot be proved to be of the same entity, its synchronous occurrence with pneumonic forms and the development of a cold agglutinin in high titer supports the contention.

Clinical Course and Duration. In any epidemic, the course of the pneumonia in individual patients is variable. Mild forms usually, but not always, predominate. In Meakins' series (214) of cases 81 per cent were regarded as mildly sick, 15 per cent moderately so and 4 per cent were severe. Among Tumulty's 93 patients, 14 per cent were "not at all ill," 68 per cent mildly so, 17 per cent moderately sick and 1 per cent severely sick (274). In others (194) all attacks were severe. In the average case the symptoms and signs increase in intensity over several days and gradually abate in several days. Patients with high fever and evidence of extensive pneumonia may not appear to be very sick, and others with minimal pulmonary involvement may be intensely so. The pulse rate and amount of sputum, as stated before, tend to increase in the later stages, as do dyspnea and cyanosis. Cough, headache or sweating may give the most distress. Inflammation may descend to the lungs, or ascend to the upper air passages. Evidence of inflammation of the upper air passages often precedes the pneumonia but may appear late in the disease. A small percentage of patients are alarmingly sick and at times appear to be moribund. In some, sudden attacks of circulatory collapse and a shock-like state appear, may recur, and may cause death. A sudden increase of fever and of other symptoms often indicates a spread of the pneumonic process. Termination is usually gradual by lysis, but may be abrupt at times (202). Complicating invasion by pyogenic bacteria is strikingly uncommon. There is often a loss of considerable weight, up to 12 Kg. (27 pounds) (131,175, 241).

The duration of the febrile period varies from 1 to 45 or more days, averaging 7 or 8 days, according to most observers. One patient (239) with pneumonia and encephalitis died on the fifty-fifth day. The period of confinement to the hospital as observed in school infirmaries and military hospitals varied from 15 to 40 or more days (see table). The disease is often prolonged by a spread of the process to other parts of the lung, by relapses, recurrences or rarely by complications.

Relapse or *recurrence* were not recorded by Gallagher (161) but according to others occur in from 2 to 10 per cent of cases (110, 181, 227, 241, 274, 276). Recurrences occur many months after the first attack (229, 290) but usually

within 2 weeks (241). There may be 2 or more recurrences (227). They usually are less severe than the first attack but may be more so. The same lobe or other lobes may be involved. Late supposed recurrences actually may be nfection by a different agent. There is no evidence that an attack of viral ipneumonia renders persons more susceptible to subsequent infections (199).

The *mortality rate* is low and is generally estimated as 0.1 per cent (155a) though figures of 2 per cent (110) and 3 per cent (204) are given. Fatalities most often occur in aged patients (290), in patients with coexisting chronic disease or from circulatory collapse.

Physical signs: Because of the range and variability of the severity of the disease, equally great variation may be expected in the physical signs. As stated before, some patients with extensive pneumonia may not appear to be very sick (94, 117, 141, 159, 174, 177) while others with minimal involvement may be intensely sick (244).

Early in the course of the attack of average severity, the face is often flushed and the conjunctivas reddened. There may be an unproductive cough. Dyspnea, tachypnea and cyanosis occur in the severest attacks. The pulse rate has been discussed. The mucous membrane of the nose and throat is dry and reddened, often intensely so. Congestion is often great enough to obstruct the nares (168, 239). Laryngoscopic and bronchoscopic examination reveal inflammation, and occasionally excoriation and crusting with especial involvement of the lymphoid follicles and tissue (75c, 212, 241). The exudate may be tenacious but is usually scanty. The vocal cords may be inflamed and thickened. The lining of the whole respiratory tract including the bronchial tree may be involved (239) or only that portion of the bronchus supplying the pneumonic area may be affected and the mucosa of the upper tract may show no changes (234). The cervical lymph nodes are seldom enlarged or tender (79, 168, 241). Several authors have reported an exanthem of various kinds (179, 193, 220, 235). Dermal eruptions may be caused by a sulfonamide drug or penicillin, if given. Jaundice was rarely noted (193, 241). Herpes according to most reports rarely occurs (193, 201, 220, 222, 227, 239), but Cutts (137) noted it in 23 per cent of cases.

Abdominal distention, so commonly present in pneumococcal pneumonia, rarely occurs (79). The spleen has been palpable in the minority of cases (193, 201, 220). There are no significant changes in the blood pressure.

The lungs: One of the characteristics of the disease is the paucity of abnormal physical signs in the lungs as compared with the amount of roentgenographic evidence of pneumonia. In some instances abnormal signs may never develop or may appear after recovery. Occasionally signs may be present without roentgen evidence of infiltration (241). Rales may be heard at some time during the disease in most patients. The signs are those of an infiltrative process, congestion or atelectasis, not of consolidation.

The earliest detectable signs during the first 2 to 4 days are suppressed breath sounds and rales in the affected area. As the lesion increases, there is impaired resonance. Dulness is rarely as pronounced as in lobar pneumonia and the

breath sounds are rarely tubular. When tubular breathing, bronchophony or egophony occur they usually indicate atelectasis. The rales are described by various terms and may be regarded as variable. Coarse rhonchi may be present. The signs in general are variable and may shift from place to place within a few hours as the pneumonia spreads or as atelectasis or emphysema appears and disappears. Showers of rales may appear from time to time. Rales and changes in the percussion note and breath sounds may be absent during the disease and appear after it is over. The signs may last a day or two or may persist for weeks, even after roentgenographic clearing, or abnormal shadows may persist with no tell-tale signs. The signs may be located anywhere in the chest or may be detected in all areas at once or in succession as the lesions migrate. The extent and degree of abnormal signs are not always a reliable index of the severity of the disease. Pleural friction and/or signs of effusion occur in a small percentage of cases, pericardial friction in fewer still.

Laboratory studies: The sputum is uncharacteristic. It is often scanty and 10 per cent of Berryhill's patients (117) raised none. The amount may increase in the later stage but it seldom exceeds 30 cc. a day. It is mucoid or mucopurulent, not tenacious. It is occasionally streaked with blood, but rarely bloody or rusty. Bacteriologic studies, except for those concerning streptococcus MG (79) and the psittacosis group of agents have failed to give diagnostic clues. Many studies have consistently failed to demonstrate a filtrable virus (75, 79). Viruses which have been encountered by others are discussed on previous pages. The bacterial flora in the sputum and in secretions removed bronchoscopically from volunteers seldom changes before, during or after the pneumonia (141). Pneumococci, of the higher numbered types may be present (79) but their absence is often notable (171, 193, 223, 239). They can seldom be detected by the direct capsule-swelling test. The sputum at times contains remarkably few bacteria of any kind (94, 202, 214, 239). Indifferent streptococci are often present (91, 120, 227, 238, 246a, 291). The exudate is often composed chiefly of polymorphonuclear cells but occasionally mononuclear cells may predominate (94, 284). Swab preparations of the pharyngeal mucosa often reveal a predominance of mononuclear cells (2).

The blood: The amount of hemoglobin and number of erythrocytes seldom diminish except in severe, prolonged attacks (104, 241). Stippled erythrocytes and Döhle bodies have been recorded (239). All reports are in agreement as to the normal or slightly abnormal number of leukocytes, and in the relative proportion of the different types of cells. Leukopenia (141, 163, 201, 206, 210, 220, 239) and leukocytosis (79, 104 196, 201, 210, 220, 239, 262, 265) may occur. Leukocytosis supposedly accompanies the infection itself (233) but may indicate bacterial invasion. The count may increase to 20,000 or more. Changes in the count have no prognostic significance. Eosinophilia (131, 215) and monocytosis have been noted (128, 131, 215, 284, 306). During experimentally induced pneumonia in volunteers (75e), there were no important changes in any of the elements.

The amount of protein in the blood seldom changes significantly (104). In one

study (148) there was no hypoaminoacidemia or excessive retention or later excretion of sodium chloride as seen in lobar pneumonia. The icterus index, prothrombin and serum CO_2 are normal, but the amount of plasma carotine and vitamin A was reduced as in other infections (79). Transitory, falsely positive Wassermann, Kahn and Eagle tests and an abnormal gold salt curve have been noted (168, 193, 196, 227, 292). Adams (104) reported a positive cephalin-cholesterol flocculation reaction in certain patients and a positive heterophile antibody reaction without important leukocytic changes in 62 per cent of his cases. Agglutinin for sheep red cells was also reported by others (277, 284, 306). The significance of these observations is uncertain. They may indicate a peculiar form of the disease or confusion with other entities.

The sedimentation rate of erythrocytes: The normal amount of protein in the blood suggests that the sedimentation rate is not greatly disturbed, yet numerous observers report an increase in the rate. It is never so great as in pneumococcal pneumonia. In Adams' (104) patients the rate averaged 19 mm. per hour; the greatest speed was 45 mm. The rate returned to normal after the twenty-second day in most patients. A rate of more than 15 mm. persists on the average for 28 days, with a range of 9 to 73 days (79). In Meakins' (214) cases the rate was normal in 62 per cent. Changes in the rate are used by some physicians (276, 281) as an aid in prognosis and management, but others (141, 214, 285) ascribe no significant value to them. There was little or no change in most of their patients.

Cold agglutination of erythrocytes: Clumping of erythrocytes in the chilled blood of a patient with pneumonia was first reported by Clough in 1915, but association of the phenomenon with viral pneumonia was generally studied only after the publications by Peterson and his associates (302), by Turner (309), by Horstman and Tatlock (296) and by Shone and Passmore (306) within a few months of each other in 1943. The reason for agglutination of homologous or of group O erythrocytes at ice-box temperature, but not at 37 C, is unknown, but the causative factor, as in the case of antibodies, seems to be associated with the globulin fraction of the blood (300). The cold agglutinin may be related to the causative agent (289).

Cold agglutination occurs in about 55 per cent of viral pneumonias (91) but considerable variation in its incidence is reported by different observers. Differences may depend partly on the technic used for the test, on the severity of the disease, and on the entity studied. In certain outbreaks, the reaction occurs in over 90 per cent of patients (300, 310) and in others, in none (104). Cold agglutination occurred in most of the induced severe and mild nonpneumonic attacks in volunteers (75). The variability of its presence in different outbreaks suggests that different etiologic entities may be operative. It does not appear in significant titer in the psittacosis group of diseases, nor in influenza (289).

The reaction usually appears during the second week of viral pneumonia and often after recovery has occurred. It reaches its highest titer during the third week. The height of the titer is generally in proportion to the severity of the symptoms, the extent of the pulmonary lesion and the duration and height of

the fever (285, 290). The average titer is between 40 and 640, but it h observed microscopically at 1:250,000 (244).

In most cases the reaction vanishes by the fourth to sixth week (290). persist for 9 months (287). Unfortunately, because of its late appeara test is of no value in early diagnosis or in deciding upon the kind of thera applied, but it is helpful in retrospective diagnosis. Cold agglutination in patients with "colds", some of which may be the mildest forms of the including viral pneumonias, and may appear and disappear in perso have not been sick, but who may have had inapparent infection (287).

It is unfortunate, too, that cold agglutination also occurs in many other such as bacterial pneumonia, scarlet fever, mumps, measles (285, 289), i matic fever, infectious mononucleosis and other diseases (299, 304 to 30 occurs less often in these diseases and usually in titer of less than Hemagglutination may take place in the blood stream to account for t chanical destruction of erythrocytes with resulting hemolytic anem thrombosis (290, 293, 304).

Several observers suspected an association between sulfonamide thera cold agglutination (286, 301) but others found no relationship (285, Hemagglutination was especially striking in pneumonic patients with r (306). Cold agglutination may be accompanied by a severe hemolyti (286, 293); by acrocyanosis (295) and by multiple thrombosis (304).

Agglutinin for streptococcus MG: Previous mention was made of the taneous appearance of cold agglutinin and agglutinin for indifferent strept in most patients with viral pneumonia. The maximum titers do not nece occur at once, nor are the reactions related to each other or to other p serologic phenomena.

Other data: The urine rarely shows changes other than those common to albuminuria (79, 104). The fluid of pleural effusion is usually thin and Occasionally cells are present with a predominance of mononuclear Empyema caused by pyogenic bacteria rarely occurs.

The cerebrospinal fluid examined in the average case without evide encephalitis shows no abnormalities (79, 91, 141) but may contain 50 ly cytes per c.mm. and give weakly positive reactions for protein (79). In patients with suspected or actual involvement of the central nervous syste leukocytes numbered between 17 and 2500; and either polymorphonucl mononuclear cells predominated. The spinal fluid pressure rose and the pr increased in amount (124, 141, 168, 179, 193, 227, 239).

Electrocardiographic changes are relatively unimportant. Changes in the segments, T waves or disturbances in conduction suggestive of pericarditi myocarditis occurred in about 4 per cent of Painton's 321 patients (229). patients with occasional transitory electrocardiographic changes are als ported (153, 158, 167, 190, 279). No significant changes of any kind detected in one series of 50 cases at any stage of the disease (79).

Roentgenologic changes: German and French roentgenologists describe monary shadows which probably were those of viral pneumonia in the 1920'

after (238), with particular regard as to their similarity to those of influenza and tuberculosis as did Arrasmith (111) in 1930, Bowen (120) in 1935 and Allen (107) in 1936. In several more recent reports of mass roentgenography on normal persons and those with mild infections of the respiratory tract, unexpected transitory shadows were frequently encountered (109, 114, 317). Becker (114) regards the shadows as evidence of atelectasis from bronchial obstruction. Andrus (109) and Kennedy (317) call them complications. Many pneumonias are detected by roentgenography alone. The pulmonary changes are remarkably like those described in measles (36). All observers, as stated in the clinical discussion, are in agreement about the usual disproportion between the roentgenographic evidence of pulmonary involvement and the sparse physical signs. It will be recalled that roentgenographic evidence of pneumonia may exist in persons who are only slightly sick (141, 156, 256, 313, 323), and some patients with profound disease may show little or no evidence of pneumonia (141, 161, 186, 244, 313), but in general the severity of the disease and amount of pulmonary involvement are proportionate. Lewis and Lusk (320), propose classifying the roentgenographic changes as bronchitis, peribronchitis, and alveolar and bronchoalveolar phases depending on their location and correlation with the pathologic changes.

Mild forms: In the mildest forms of viroid or the acute disease of the respiratory tract of which viral pneumonia is a part, abnormal densities are found occasionally when roentgenograms are made at intervals (109, 114, 141, 156, 238, 256, 313, 317, 323); in some studies in 25 per cent of cases (320).

Moderately severe forms; tracheobronchitis: In one series of 86 patients classified as having moderately severe disease, roentgenographic evidence of tracheobronchitis occurred in 24 and of pulmonary invasion in 22 (318). In most of the patients, rales were heard over the large bronchi or in the interscapular areas. There was increased prominence of the normal hilar and truncal shadows on one or both sides, probably caused by infiltration and congestion in and around the bronchial and peribronchial structures (318, 320). Certain patients with no more involvement than this may be severely sick (94, 244). The shadows are usually transitory and disappear in a week or two.

Pneumonic cases: Shadows in the lung may appear as early as 24 hours after the onset of disease, but usually not until after the third or fourth day. In experimentally induced pneumonia (75e) evidence of invasion appeared from the second to the fifth day of disease, usually on the fourth. Shadows are first those of tracheobronchitis, as just described, with ill defined, blurred localized structural accentuation (313, 318). The density then extends peripherally in streaks along the large tubes, or veil-like in the shape of wedge fading into the parenchyma and partly obscuring a portion, or less often, the whole of a lobe, in harmony with the interstitial nature of the pneumonia. Occasionally the density first appears in the parenchyma and spreads radially. A shadow may remain in one area, but characteristically spreads in the lobe or migrates to other lobes or appears in the other lung, until all areas may be obscured either at once or in succession. Various adjectives describe the densities as ground-glass-like,

cottony, downy, fleecy, patchy, soft, granular, flocculent, nodular and homogeneous; all are appropriate at times. The shadow is rarely as dense as that of pneumococcal pneumonia, although only a single lobe may be involved. The density is usually greatest near the hilum. The accentuated structual markings are usually visible through the density. Scattered areas of pneumonia may *coalesce*.

The shadows may disappear in 3 or 4 days but usually persist for 3 or 4 weeks (79, 141) and sometimes longer (319). The shadows may appear and disappear in a few hours. Evidence of resolution takes place in the reverse order, structural intensification being the last sign to disappear (313a). Shadows in some cases continue to increase in size and density after clinical recovery has taken place (323). Mottled densities suggestive of a lobular form of atelectasis or of collapse of a lobe from obstruction of airways are commonly present (313, 314). The mediastinum is occasionally shifted to the affected side and the diaphragm raised (124). Local areas of emphysema are noted (314).

The lobes chiefly affected are the same as those of lobar pneumonia. The lower lobes are involved in 80 per cent of cases in most reported studies. Involvement of several lobes occurs in 10 to 20 per cent of cases. In 13 per cent the process remains localized in the hilar region (141).

While roentgenography is of great aid in detecting the presence and following the course of the pneumonia, it cannot be relied upon alone for diagnosis or for differentiation. The shadows cast by viral pneumonias are indistinguishable from those caused by pulmonary infection with rickettsia or fungi, by sarcoidosis, atelectasis, passive congestion, neoplastic infiltration, early localized or miliary pulmonary tuberculosis, at times by pneumococcal and other bacterial pneumonias, and other conditions (256, 320, 324).

In some studies pleural effusion was not encountered (141, 313, 320) and in others evidence of it was seen in 6 per cent of cases (124). Dilated bronchi as visualized by some, suggest bronchiectasis (313) but the change is usually transitory (pseudobronchiectasis) (119). Fractures of ribs are reported (124, 316) as probably caused by violent coughing. Fractures may account for severe pleural pain in some instances mistaken for pleurisy.

Complications. Almost all observers comment on the scarcity of complications in viral pneumonia as compared with influenza, for example. On the other hand, there is confusion as to what constitutes a complication. Some observers wrongly include integral features of the disease as complications such as pleural effusion, delayed resolution and severe headache. Others include preexisting conditions or coincidental ones. The incidence of recorded complications varies from zero, 7 per cent (229), 27 per cent (204), 37 per cent (276) to 42 per cent (181). Higley (181) included recurrences, atelectasis, pleural pain and asthma to account for complications in 42 per cent of "proved cases". Van Ravenswaay (276) reports pleural effusion, empyema, bronchiectasis, hemoptysis and urethritis which he believes can be largely avoided by prolonged convalescence in bed. Lyght (204) observed pleural effusion, acute otitis media, sinusitis, massive atelectasis, tonsillitis, myocarditis, pneumothorax, pericarditis, cystitis and infectious mononucleosis in his series of patients. Owen (227) noted pleural

effusion in 4 per cent. Kay (191) noted ulcerative lesions in the bronchial tree in 9 patients and believes that bronchiectaisis often follows viral pneumonia which according to other studies is not the case. Glendy (163) encountered abscess of the lung and extreme leukopenia. Several observers record both clinical and electrocardiographic evidence of pericarditis, others electrocardiographic evidence alone (153, 158, 279). Cardiac enlargement (168) and toxic myocarditis (270) have been noted. Peripheral circulatory collapse may occur and recur during the course and may be fatal (217, 239). It may recur during convalescence (276). Pneumococcal lobar pneumonia (79, 241, 271) and bacteremia (250, 290) rarely occurred as complications or sequels. Ribs may be fractured by coughing (124, 316).

Encephalitis and meningomyelitis have been noted clinically and at necropsy (75e, 124, 164, 168, 179, 182a, 185, 193, 231, 239, 257). They are likely to be a part of the disease but may be nonspecific toxic reactions or caused by a complicating agent. Encephalomyelitis, toxic psychosis and pleural effusion occurred in 3 volunteers with experimentally induced viral pneumonia (75e). Toxic neuronitis was noted (223). Other less commonly recorded occurrences are polyneuritis (182a), stomatitits (79), purulent empyema (227), relighting of old tuberculosis (206), hemoptysis (144), otitis media (79, 246a), tonsillitis, sinusitis (79, 241), thrombophlebitis (190, 290). Jaundice in a few cases may have been caused by viral hepatitis (241). Severe mucocutaneous eruptions may be those of erythema multiforme exudativum with pneumonia (129a, 205).

Several clinicians have observed acute hemolytic anemia (286, 290, 293, 296, 302, 304), thrombosis (304) and acrocyanosis (295) usually associated with cold agglutination in high titer. Complications occurring in patients treated with sulfonamide drugs should not be confused with those of the disease itself.

Viral pneumonia as a complication: Patients with other disease, of course, can contract pneumonia. Owen (227) reports its occurrence post-operatively, during pregnancy, asthma, bronchiectasis, scarlet fever, and in heart disease during which 3 deaths occurred. Pneumonia occurred in patients with malaria (110a, 123, 154, 274, 306), chronic rheumatic heart disesae (187, 201, 211, 290) and viral hepatitis (274).

Diagnosis. Since the cause is unknown and because several entities probably compose the syndrome described as viral pneumonia, there are no specific diagnostic aids. Early diagnosis at present depends upon the epidemiologic and clinical aspects of the disease, supported by appropriate laboratory tests and roentgenography as described in previous pages. The especial value of roentgenography has been emphasized. The presence of an epidemic of mild disease is helpful, but early diagnosis in isolated, sporadic severe viral pneumonias is not easy. A normal or slightly abnormal leukocyte count and sedimentation rate are helpful in diagnosis. Late in the disease, or after it is over, the cold hemagglutination test and the agglutination test for streptococcus MG are positive in a large percentage of cases and aid in retrospective diagnosis. The lack of clinical response to sulfonamide compounds (170, 171) and to penicillin also aids in retrospective diagnosis but cannot be depended upon (236).

Differential Diagnosis. The group of diseases in which viral pneumonias occur,

such as colds, pharyngitis, bronchitis, grip, febrile catarrh and viroid, but for a few clinical characteristics can seldom be differentiated (246). They can be separated from infections of known cause like influenza and of the psittacosis group by specific tests. The same is true for other diseases which are often clinically indistinguishable from viral pneumonia such as coccidioidomycosis, Q fever, and toxoplasmosis. Diagnosis in coccidioidomycosis and in Q fever is also aided by epidemiologic factors, the demonstration of the causative agents and immunologic evidence of their operation. Early pulmonary tuberculosis is especially confusing when the upper lobes are involved (195, 278a, 282, 283). Diagnosis is established by the presence of *M. tuberculosis*, the clinical course and evidence of previous contact with the disease. Brucellosis with its normal leukocyte count, sweating and cough may be suspected. Malaria (110a, 123, 154, 176), dengue fever (274) and measles may cause confusion until their characteristics become evident. Loeffler's syndrome or allergic pneumonia is characterized by eosinophilia or other allergic phenomena. Infectious mononucleosis is recognized by hematologic changes, and enlargement of the lymph nodes and spleen (104, 171, 277, 284). Rheumatic pneumonia rarely causes confusion (187, 211). Neoplastic infiltration of the lung, atelectasis, pulmonary fibrosis, passive congestion, and bronchiectasis may for a time be suspected.

The severe, isolated attacks of viral pneumonias resemble typhoid fever, psittacosis-ornithosis (17, 238), tuberculosis and tularemic pneumonia. These may be recognized by epidemiologic data, the course of the disease, and by the identification of the causative agents or serologic evidence of their presence. Cold agglutination even in low titer seldom occurs in these diseases. It is important to establish the diagnosis of the psittacosis group of infections promptly since there is evidence of their response to therapy with penicillin Severe eruption of the skin and oral mucous membrane occurs with the pneumonia of erythema multiforme exudativum (129a, 205).

Perhaps the most important aspect of differentiation concerns the bacterial pneumonias in which early therapy with penicillin, streptomycin or sulfadiazine is mandatory (112). It has been known for years that different bacteria may cause "primary atypical pneumonia" in the original sense of the term (127) which in many cases is clinically indistinguishable from the viral pneumonias discussed here (236, 284a). Diagnosis may be uncertain in the viral pneumonias if pneumococci, streptococci or staphylococci or other bacteria are present in large numbers in the sputum. The problem is especially difficult when indifferent streptococci predominate. In cases of viral pneumonia diagnosed by the development of cold agglutinin in high titer, various bacteria are present as commensals (141) or they may become invasive and cause a complicating infection (236, 258). Any of the bacteria may, of course, be the "primary" cause of pneumonia. Pneumococci, especially of the low numbered types, in the sputum and/or in blood strongly indicates their etiologic significance. Pneumococci of other types are commonly found as saprophytes, but may also cause pneumonia (258). Roentgenographic changes, clinical signs of consolidation,

herpes, the leukocyte count, bradyeardia and lack of response to sulfonamide drugs or to penicillin cannot be depended upon for differentiation (236). The diagnosis of pneumococcal pneumonia may be obscured if bacteriologic tests are made after sulfonamide chemotherapy which often eliminates pneumococci from the sputum (144) and modifies the clinical course. Diagnosis of the atypical pneumococcal pneumonias may be made in retrospect by the demonstration of specific agglutinins for the causative pneumococcus (236, 284a) or by skin tests with specific polysaccharides.

Symptoms of involvement of the nervous system may raise the questions of bacterial or viral meningitis or encephalitis. Abdominal pain may suggest appendicitis (168, 227).

Prevention. The isolation of patients and masks and gowns worn by attendants are theoretically desirable because of the likelihood of airborne contagion (104, 212, 217, 241, 262, 284). Yet as in other acute diseases of the respiratory tract, these measures are often futile (141, 214) unless rigidly enforced. Absolute measures of isolation are generally impractical or impossible. Furthermore, by the time an epidemic is recognized and measures can be brought to bear, it is usually too late. The agent is already widely disseminated because of the long incubation period, the large number of ambulant patients with mild disease and the probable existence of persons with inapparent infection (141) who escape control. Close and continuous contact with patients having disease of any degree of severity obviously should be avoided if possible. There is no evidence that infection may be transmitted by utensils, fomites or other means. No reports have appeared about the prevention of airborne infection of viral pneumonia as such with aerosols or with ultraviolet light, but other mild respiratory tract diseases have been controlled by these measures. There are no other known effective preventive procedures except for measures to maintain health (246). Chilling (141), fatigue (151) and malnutrition should be avoided on general principles.

Treatment. Patients with the mildest attacks usually refuse to go to bed and thereby serve as migratory spreaders of infection. Patients who have fever should be kept in bed with nursing attention. Medication is not needed in the majority of cases except for mild vasoconstrictor drugs to relieve nasal congestion; relatively humid, cool air for cough, and mild analgesics for headache or aching, unless they cause additional diaphoresis (246).

Severe attacks obviously require more care. Bed rest is essential. The diet is usually of no great importance in the average case of brief duration so long as it is abundant, varied and adequate in calories and vitamins (284). Fluids need not be given to excess unless severe sweating occurs, when sodium chloride also should be supplied (131, 217, 284). Alkalinization is superfluous (246).

Fever: Tepid sponge baths and cool compresses applied to the head give comfort, and are helpful if delirium occurs. Antipyretic drugs should not be used since they add to the discomfort caused by sweating and increase the loss

of water (141, 150, 241). There are no satisfactory measures to inhibit sweating. Atropine sulfate is sometimes effective, but may cause unpleasant side effects. The clothing and bedding should be changed when wet. Repeated changing may be needed.

Cough: The cough is often resistant to all forms of treatment. The commonly employed traditional cough syrups and the supposed expectorant drugs seldom serve their purpose (150, 246, 284) and often cause digestive disturbance. Since exudation is not a characteristic of the disease, there is little logic in trying to provoke it. If the sputum is tenacious and annoying, its expulsion may be aided by the inhalation of 5 per cent carbon dioxide to increase the depth of respiration (222). This measure may also prevent atelectasis. Oxygen inhalation has been recommended for cough but its use is not logical for this purpose. The simplest methods of relieving paroxysmal cough are rest and quiet, and lozenges containing methol or other volatile oils dissolved slowly on the tongue. Dryness can be relieved by cooling the atmosphere and humidification with a water vaporizer (227, 241). Spraying the dry, inflamed membranes of the nose and throat occasionally with warm, isotonic solution of sodium chloride gives comfort. If these measures fail, codeine sulfate in 0.03 to 0.06 Gm. ($\frac{1}{2}$ to 1 grain) doses given every few hours as needed is helpful. In the severest cases 0.5 cc. of 0.5 per cent p-chlorphenol in liquid petrolatum injected deeply into the larynx and trachea with a curved-tip syringe gives relief for several hours. As a last resort, morphine sulfate may be needed to provide relief and sleep. A cloth binder applied across the lower part of the chest and upper part of the abdomen and tightened to suit comfort relieves the soreness of muscles incident to coughing. In rare instances in which profuse expectoration occurs, postural drainage is helpful (141, 191, 284). Atropine is not recommended.

Pain in the chest is relieved with a binder or with applied heat (204). Adhesive tape should not be used. Headache is often aggravated by coughing. It is treated with cool compresses and codeine; aspirin may be tried if diaphoresis is not too great. When severe headache and other signs suggest encephalitis, withdrawal of spinal fluid is helpful if the pressure is increased (141d).

Oxygen inhalation is recommended for dyspnea and cyanosis (204, 227, 241, 285). Circulatory failure is treated by appropriate methods which, incidentally, are seldom effective (146). The so-called cardiac stimulants such as camphor, caffeine, strychnine, coramine and others are of little or no value. Digitalis is not needed except for certain forms of heart failure and auricular fibrillation during the disease (141d).

Local treatment with swabs, gargles and sprays of medicated solutions is anachronistic (246). Nasal congestion may be lessened temporarily by the inhalation or the application of convenient aqueous preparations of amphetamine (benzedrine), 2-aminoheptane (tuamine), naphazoline hydrochloride (privine), ephedrine, epinephrine or related compounds (141d).

Special measures: Sulfónamide compounds have no influence in viral pneumonias, and except for one report (259) all observers agree that penicillin is likewise of no value in treatment (108). Sulfonamide compounds are said to

make the patient feel worse (110). It is doubtful whether these agents should even be used as prophylaxis against secondary bacterial invasion which so seldom occurs. The actual development of complications caused by certain bacteria, of course, demands prompt, vigorous antibiotic treatment.

In many instances, however, early differential diagnosis from the bacterial or psittacotic pneumonias is doubtful or impossible to make. When uncertainty occurs, appropriate specimens for etiologic diagnosis should be collected before the prompt application of penicillin, streptomycin, or sulfadiazine according to the need (273) in adequate, controlled dosage. If, after a reasonable time, up to 72 hours, no benefit takes place or if bacterial infection can be ruled out, therapy should be stopped (284).

Roentgen-ray therapy: Although experimental studies in animals (113) and a few clinical reports (133, 225, 226) suggest that roentgen-ray therapy in the earliest stages of the disease tends to shorten its course, the clinical evidence therefor is inconclusive. If treatment actually shortens the duration of disease or lessens its severity it is of value, but not if it simply hastens the resolution of the abnormal shadows in the lung which are of little importance.

Convalescent serum has been recommended (246a) and used (155, 189, 231, 265, 278), but here too, the results suggesting benefit are unconvincing (94, 110, 208, 284). Convalescent serum has no significant specific curative value in any infectious disease.

Transfusion of blood or of plasma has been advocated from time to time especially for severe attacks (189, 206, 208, 222), but unless anemia or hypoproteinemia is present, it is not needed (168, 193, 227, 284). Fluids injected intravenously are not of much help for circulatory collapse either (146).

Neoarsphenamine (167) and quinine (123) are of no value.

Convalescence. Convalescence is usually rapid and uneventful but some observers mention asthenia (227), prolonged disability (276) and mental depression (284) as sequels. Convalescence in one series of patients usually required 10 to 15 days, occasionally 40 days.

Rest in bed for a week or two after moderately severe attacks is usually sufficient before activity is resumed; longer periods are needed after severe attacks or if complications or other reasons demand it (229). Since abnormal roentgenographic densities in the lung occasionally persist for weeks, patients' activities need not be restricted for this reason alone (144). The return of the sedimentation rate to normal has been advocated as a criterion for resuming activity (276, 281) but if the rate stays above normal for some time, as it may, it would induce needless restriction. According to two observers recurrences were reduced from 25 per cent to 2.5 per cent and confinement in the hospital was shortened from 55 to 35 days by increasing convalescent bed rest from 4 to 14 days and employing graded training (273, 276). Recurrences, relapses, circulatory collapse and death may occur during convalescence.

Iron therapy may be given if anemia is present. Deep breathing exercises, sunbaths and graded physical exercise are helpful in restoring health (104, 227).

REFERENCES ON THE VIRAL PNEUMONIAS

1. Adams, J. M., Thigpen, M., and Rickard, E. R.: An Epidemic of Influenza A in Infants and Children. J. A. M. A. **125**: 473–476 (June 17) 1944.
2. Adams, J. M., Pennoyer, M. M., and Whiting, A. M.: Pathologic Study of the Acutely Inflamed Human Pharynx in Influenza A Infection. Am. J. Dis. Child. **71**: 162–170 (Feb.) 1946.
3. Armstrong, C., and Lillie, R. D.: Vaccine Virus Pneumonia in Rabbits. Pub. Health Rep. **44**: 2635, 1929.
4. Baker, J. A.: A Virus Obtained from a Pneumonia of Cats and Its Possible Relation to the Cause of Pneumonia in Man. Science **96**: 475–476 (Nov. 20) 1942. A Virus Causing Pneumonia in Cats and Producing Elementary Bodies. J. Exper. Med. **79**: 159–172 (Feb.) 1944.
5. Beck, M. D., and Eaton, M. D.: Identification of Two Strains of Virus Isolated from Cases of Atypical Pneumonia. J. Inf. Dis. **71**: 97–101 (Sept.–Oct.) 1942.
6. Beck, M. D., Eaton, M. D., and O'Donnell, R.: Further Laboratory Studies in the Classification of Psittacosis-Like Agents. J. Exper. Med. **79**: 65–77 (Jan.) 1944.
7. Borrell, A.: Epitheliosis infectieuses et épitheliomas. Ann. Inst. Pasteur, **17**: 81–122 (Jan.) 1903.
8. Bosc, F. J.: Les epitheliomas parasitaires. La clavelée et l'epithelioma claveleux. Centralbl F. Bakt. (Abt. 1) **34**: 517–526, 1903.
9. Bullowa, J. G. M., and Wishik, S. M.: Complications of Varicella. Am. J. Dis. Child. **49**: 923–932 (April) 1935.
10. Corbett, E. V.: The Visceral Lesions in Measles. Amer. J. Path. **21**: 905–914 (Sept.) 1945.
11. Cowdry, E. V., and Marsh, H.: Comparative Pathology of South African Jagziekte and Montana Progressive Pneumonia of Sheep. J. Exper. Med. **45**: 571–585 (Apr.) 1927.
12. DeBurgh, P., Jackson, A. V., and Williams, C.: Spontaneous Infection of Laboratory Mice with a Psittacosis-Like Organism. Australian J. Exper. Med. **23**: 106–108 (June) 1945.
13. Eaton, M. D., Beck, M. D., and Pearson, H. E.: A Virus From Cases of Atypical Pneumonia. Relation to the Viruses of Meningopneumonitis and Psittacosis. J. Exper. Med. **73**: 641–653 (May) 1941.
14. Eaton, M. D., and Corey, M.: Complement-Fixation in Human Pneumonitis with Group-Reactive Virus Antigens. Proc. Soc. Exper. Biol. & Med. **51**: 165–168 (Oct.) 1942.
15. Eaton, M. D.: Serological Differentiation of Primary Atypical Pneumonia from Virus Pneumonia of the Psittacosis Group. Proc. Soc. Exper. Biol. & Med. **60**: 231–235 (Nov.) 1945.
16. Farmer, T., and Janeway, A.: Infections with the Virus of Lymphocytic Choriomeningitis. Medicine **21**: 1, 1942.
17. Favour, C. B.: Ornithosis (Psittacosis). A Report of Three Cases, and a Historical, Clinical and Laboratory Comparison of Human Atypical (Virus) Pneumonia. Am. J. Med. Sci. **205**: 162–187 (Feb.) 1943.
18. Feyrter, F.: Ueber die Masern Pneumonie. Virch. Arch. F. Path. Anat. **255**: 753 (Aug.) 1924.
19. Finland, M., and Dingle, J. H.: Virus Pneumonias. I. Pneumonias Associated with Known Non-Bacterial Agents: Influenza, Psittacosis and Q Fever., N. Eng. J. Med. **227**: 342–350 (Aug. 27) 1942.
20. Finland, M., and others: Acute Myocarditis in Influenza A Infection. Amer. J. Med. Sci. **209**: 455–468 (Apr.) 1945.
21. Finland, M., and others: Influenza Virus Isolation and Serological Studies Made in Boston During the Winter of 1943, 1944. J. Clin. Invest. **24**: 192–208 (Mar.) 1945.
22. Fite, G. L., Larson, C. L., and Olson, B. J.: An Epidemic of Severe Pneumonitis

in the Bayou Region of Louisiana. VII. Histopathology in Laboratory Animals Pub. Health Rep. 61: 1100–1115 (July 26) 1946.

22a. Francis, T., and Magill, T. P.: An Unidentified Virus Producing Acute Meningitis and Pneumonitis in Experimental Animals. J. Exper. Med. 68: 147–160 (Aug.) 1938.

23. Francis, T., and Stuart-Harris, C. H.: Studies on the Nasal Histology of Epidemic Influenza Virus in the Ferret. J. Exper. Med. 68: 813–830 (Dec.) 1938.

24. Foreign Letters. Roentgenographic Appearance of the Lungs in Measles. J. A. M. A. 112: 345 (Jan. 28) 1939.

25. Gönnert, R.: Über ein neues Erreger des Lymphogranuloma Inguinale ähnliches Mausevirus. Klin. Woch. 20: 76–78, 1941.

26. Hare, R., Hamilton, J., and Feasley, W. R.: Influenza and Similar Respiratory Infections in a Military Camp over a Period of Years. Canad, J. Pub. Health 34: 442–452, 1943.

27. Hare, R., and others: Influenza Amongst Immunized and Unimmunized Populations in 1943. Canadian J. Pub. Health 34: 442–452, 1943.

28. Hayes, G. S., and Hartman, T. L.: Lymphocytic Choriomeningitis. Bull. Johns Hopkins Hosp. 73: 275–286, 1943.

29. Heilman, F. R., and Herrell, W. E.: Penicillin in the Treatment of Experimetal Ornithosis. Proc. Staff Meet. Mayo Clin. 19: 57–65 (Feb. 9) 1944. Penicillin in the Treatment of Experimental Psittacosis. Ibid. 19: 204–207 (Apr. 19) 1944.

30. Henle, W., and Henle, G.: The Toxicity of Influenza Virus. Science 102: 398–400 (Oct. 19) 1945.

31. Himmelweit, F.: Influenza Virus B Isolated from a Fatal Case of Pneumonia. Lancet 2: 793–794, 1943.

32. Howat, H. T., and Arnott, W. M.: Outbreak of Pneumonia in Smallpox Contacts. Lancet 2: 312 (Sept. 2) 1944.

33. Jackson, W. P. V.: Influenza B Among West Indians. Lancet 2: 631–635 (Nov. 2) 1946.

34. Karr, H. V.: Study of a Latent Pneumotropic Virus of Mice. J. Inf. Dis. 72: 108–116, 1943.

35. Koester: Mssern Pneumonie. Deutsche Med. Wochschr. 24: 8, 1898.

36. Koihn, J. L., and Koiransky, H.: Successive Roentgenograms of the Chest of Children During Measles. Amer. J. Dis. Child. 38: 258–270, 1929.

37. Larson, C. L., and Olson, B. J.: An Epidemic of Severe pneumonitis in the Bayou Region of Louisiana. Pub. Health Rep. 61: 69–78 (Jan. 18) 1946. Olson, B. J., and Treutino, W. L.: An Epidemic of a Severe Pneumonitis in the Bayou Region of Louisiana. I. Epidemiological Study, Pub. Health Rep. 59: 1299–1311 (Oct. 6) 1944. Treutino, W. L., and Olson, B. J.: II. Clinical Features. Ibid. 59: 1331–1356 (Oct. 13) 1944. Binford, C. H., and Hausen, G. H.: III. Pathological Observation. Ibid. 59: 1363–1373 (Oct. 13) 1944. Olson, B. J., and Larson, C. L.: IV. A Preliminary Note on Etiology, ibid. 59: 1373–1374 (Oct. 20) 1944.

38. Lillie, R. D., and Armstrong, C.: The Pathology of Generalized Vaccinia in Rabbits. Nat. Inst. Health Bull. No. 156, 1–95, 1930.

39. Lillie, R. D.: Smallpox and Vaccinia. The Pathologic Histology. Arch. Path. 10: 241–291 (Aug.) 1930.

40. Loosli, C. G.: The Pathogenesis and Pathology of Experimental Air-borne Influenza A Virus Infection in Mice. Fed. Proc. Amer. Soc. Exp. Biol. 5: 225 (Feb.) 1946.

40a. Lucchesi, P. F., and others: Varicella Neonatorum. Am. J. Dis. Child. 73: 44–54 (Jan.) 1947.

41. MacCallum, W. G.: Pathology of Pneumonia in the U. S. Army Camps during the Winter of 1917–1918. Rockefeller Inst. Monograph No. 10.

42. McCordock, H. A., and Muckenfuss, R. S.: The Similarity of Virus Pneumonia in Animals to Epidemic Influenza and Interstitial Bronchopneumonia in Man. Amer. J. Path. 9: 221–251, 1933 (March).

43. McNaught, J. B.: Virus Pneumonia: A Review of the Pathology, California and West. Med. 59: 220–224, 1943.
44. Meyer, K. F.: The Ecology of Psittacosis and Ornithosis. Medicine 21: 175–266, 1942.
44a. Meyer, K. F., and Eddie, B.: The Knowledge of Human Virus Infections of Animal Origin, J. A. M. A. 133: 822–828 (Mar. 22) 1947.
45. Milles, G.: Pneumonia (With a Note on the Giant Cell of Measles). Amer. J. Clin. Path. 15: 334–338 (Aug.) 1945.
46. Meiklejohn, G., Beck, M. D., and Eaton, M. D.: Atypical Pneumonia Caused by Psittacosis-Like Viruses. J. Clin. Invest. 23: 167–175 (March) 1944.
47. Muckenfuss, R. S., McCordock, H. A., and Harter, J. S.: A Study of Vaccine Virus Pneumonia in Rabbits. Amer. J. Path. 8: 63–71 (1932).
48. Nauen, R., and Korns, R. F.: A Localized Epidemic of Acute Miliary Pneumonitis Associated with the Handling of Pigeon Manure. Proc. Amer. Pub. Health Assoc. New York (Oct. 3) 1944.
49. Nigg, C., and others: Study of an Epidemic of Influenza B. Amer. J. Hyg. 35: 265-284, 1942.
50. Nigg, C.: An Unidentified Virus which Produces Pneumonia and Systemic Infection in Mice, Science 95: 49, 1942.
51. Nigg, C., and Eaton, M. D.: Isolation from Normal Mice of a Pneumotropic Virus which Forms Elementary Bodies, J. Exp. Med. 79: 497–509, 1944.
52. Parker, R. F.: Psittacosis as a Cause of Atypical Pneumonia: Penicillin Therapy, Ohio State Med. J. 41: 1097–1098 (Dec.) 1945.
53. Parker, F.; Jolliffe, L. S.; Barnes, M. W., and Finland, M.: Pathologic Findings in the Lungs of Five Cases from which Influenza Virus was Isolated, Am. J. Path. 22: 797–820 (July) 1946.
54. Pollard, M.; Kalkstein, M., and Livesay, H. R.: The Influenza Epidemic of 1943–1944 in San Antonio, Texas, Amer. J. Trop. Med. 26: 141–143 (Jan.) 1946.
54a. Pollard, M.: Ornithosis in Sea-Shore Birds, Proc. Soc. Exper. Biol. & Med. 64: 200–202 (Feb.) 1947.
55. Rake, G., Eaton, M. D., and Shaffer, M.: Similarities and Possible Relationship Among Viruses of Psittacosis, Meningopneumonitis and Lymphogranuloma Venereum. Proc. Soc. Exper. Biol. & Med. 48: 528–531, 1941.
56. Rake, G., Jones, H., and Nigg, C.: Sulfonamide Chemotherapy of Mouse Pneumonitis, Meningopneumonitis and Lymphogranuloma Venereum. Proc. Soc. Exper. Biol. & Med. 49: 449–452, 1942.
57. Rake, G.; Alexander, R., and Hamre, D. M.: The Relationship of The Agent of Heart-Water Fever—Rickettsia Ruminatium, Science 102: 424–425 (Oct. 26) 1945.
58. Rasmussen, A. A.: Primary Epidemic Alveolar Pneumonia, Ugeskr. f. Laeg. 98: 691–693 (June 28) 1934.
59. Rausch, L. E.; Grable, T. J., and Musser, J. H.: Atypical Pneumonia Complicating Severe Varicella in an Adult, New Orleans M. and S. J. 96: 271–275 (Dec.) 1943.
60. Reimann, H. A.: The Pneumonias, W. B. Saunders Co., Phila. 1938.
61. Scadding, J. G.: Lung Changes in Influenza, Quart. J. Med. 6: 425–466 (Oct.) 1937.
62. Shope, R. E.: The Influenzas of Swine and Man, Medicine 15: 453–487 (Dec.) 1936.
63. Smadel, J. E.: Atypical Pneumonia and Psittacosis, J. Clin. Invest. 22: 57–66 (Jan.) 1943.
64. Smadel, J. E.; Green, R. H.; Paltauf, R. M., and Gonzales, T. A.: Lymphocytic Choriomeningitis: Two Human Fatalities Following an Unusual Febrile Illness, Proc. Soc. Exper. Biol. & Med. 49: 683–686, 1942.
65. Smadel, J. E.; Wall, M. J., and Gregg, A.: An Outbreak of Psittacosis in Pigeons Involving the Production of Inclusion Bodies and Transfer of the Disease to Man, J. Exper. Med. 78: 189–203 (Sept.) 1943.
66. Smadel, J. E., Jackson, E. B., and Harman, J. W.: A New Virus Disease of Pigeons. J. Exper. Med. 81: 385–398, 1945.

67. Stuart-Harris, C. H.: Influenza Epidemics and the Influenza Viruses, Brit. Med. J. 1: 209-216 (Feb. 17); 251-254 (Feb. 24), 1945.
68. Thomas, L., and Kold, E. M.: Relationship of the Virus of Cat Pneumonia (Baker) to the Psittacosis-Lymphogranuloma Group of Agents, Proc. Soc. Exper. Biol. & Med. 54: 172-174 (Nov.) 1943.
69. Turgasen, F. E.: Human Ornithosis Treated with Penicillin, J. A. M. A. 126: 1150-1151 (Dec. 30) 1944. Flippin, H. F.; Gaydosh, M. J., and Fittipoldi, W. V.: Penicillin for Human Psittacosis, ibid. 127: 280-281 (May 26) 1945.
70. Turnbull, H. M., and McIntosh, J.: Encephalo-Myelitis Following Vaccination, Brit. J. Exper. Path. 7: 181-187, 1926.
71. Wanino, J. J.; Nduberger, K., and Geever, E. F.: Severe Forms of Chickenpox in Adults, Arch. Int. Med. 69: 384-408, 1942.
72. Reference deleted.
73. Wood, W. H., and Felson, H.: A Case of Lymphogranuloma Venereum Associated with Atypical Pneumonia, Ann. Int. Med. 24: 904-907 (May) 1946.
74. Zichis, J., and Shaughnessy, H. J.: Isolation of an Apparently New Virus from Two Fatal Pneumonia Cases, Science 102: 301-302 (Sept. 21) 1945.

REFERENCES ON ETIOLOGIC STUDIES

75. (a) Abernethy, T. J.: An Experimental Attempt to Transmit Primary Atypical Pneumonia in Human Volunteers. Abst. J. Clin. Invest. 23: 951 (Nov.) 1944. (b) Commission on Acute Respiratory Diseases: An Experimental Attempt to Transmit Primary Atypical Pneumonia in Human Volunteers. J. Clin. Invest. 24: 175-188 (Mar.) 1945. (c) Commission on Acute Respiratory Diseases: Transmission of Primary Atypical Pneumonia to Human Volunteers, J. A. M. A. 127: 146-149 (Jan. 20) 1945. (d) Dingle, J. H.: Present Status of Etiology of Primary Atypical Pneumonia, Bull. N. Y. Acad. Med. 21: 235-262 (May) 1945. (e) Commission on Acute Respiratory Diseases. The Transmission of Primary Atypical Pneumonia to Human Volunteers. Bull. Johns Hopkins Hospital 79: 97-167 (Aug.) 1946.
76. Andrewes, C. H., and Glover, R. E.: Grey Lung Virus. Brit. J. Exper. Path. 26: 379-386, 1945.
77. Blake, F. G., Howard, M. E., and Tatlock, H.: Feline Virus Pneumonia and Its Relation to Some Cases of Primary Atypical Pneumonia in Man. Yale J. Biol. & Med. 15: 139-166 (Dec.) 1942.
78. Curnen, E. C.: Symposium on Primary Atypical Pneumonia. Soc. Am. Bacteriologists, General Meeting, N. Y., May, 1944.
79. Curnen, E. C., and others: Studies on Primary Atypical Pneumonia: I. Clinical Features and Results of Laboratory Investigation. J. Clin. Invest. 24: 209-226 (March) 1945.
80. Dammin, G. J., and Weller, T. H.: Attempts to Transmit Primary Atypical Pneumonia and other Respiratory Tract Infections to the Mongoose. J. Immunol. 50: 107-114 (Feb.) 1945.
81. Dochez, A. R., Mills, K. C., and Mulliken, B.: A Virus Disease of Swiss Mice Transmissible by Intranasal Inoculation. Proc. Soc. Exp. Biol. & Med. 36: 683-686 (June) 1937.
82. Eaton, M. D., and others: An Infectious Agent from Cases of Atypical Pneumonia Apparently Transmissible to Cotton Rats. Science 96: 518-519 (Dec. 4) 1942.
83. Eaton, M. D.: Virus Pneumonia: Etiologic Studies. California and West. Med. 59: 160-161 (Sept.) 1943.
84. Eaton, M. D., and VanHerick, W.: Demonstration in Cotton Rats and Rabbits of a Latent Virus Related to Pneumonia Virus of Mice. Proc. Soc. Exp. Biol. & Med. 57: 89-92 (Oct.) 1944.

85. EATON, M. D., MEIKLEJOHN, G., AND VANHERICK, W.: Studies on the Etiology of Primary Atypical Pneumonia: A Filtrable Agent Transmissible to Cotton Rats, Hamsters and Chick Embryos. J. Exper. Med. **79:** 649–688 (June) 1944.
86. EATON, M. D., AND OTHERS: Studies on the Etiology of Primary Atypical Pneumonia. II. Properties of the Virus Isolated and Propagated in Chick Embryos. J. Exper. Med. **82:** 317–328 (Nov.) 1945.
87. EATON, M. D., AND OTHERS: III. Specific Neutralization of the Virus by Human Serum, J. Exper. Med. **82:** 329–342 (Nov.) 1945.
87a. EATON, M. D., AND VAN HERICK, W.: Serological and Epidemiological Studies on Primary Atypical Pneumonia and Related Acute Upper Respiratory Disease, Am. J. Hyg. **45:** 82–95 (Jan.) 1947.
88. GORDON, F. B., FREEMAN, G., AND CLAMPIT, J. M.: A Pneumonia-Producing Filtrable Agent from Stock Mice. Proc. Soc. Exp. Biol. & Med. **38:** 450–453, 1938.
89. HORSFALL, F. L., AND HAHN, R. G.: A Pneumonia Virus of Swiss Mice. Proc. Soc. Exp. Biol. & Med. **40:** 684–686 (Apr.) 1939.
90. HORSFALL, F. L., AND OTHERS: A Virus Recovered from Patients with Primary Atypical Pneumonia. Science **97:** 289–290 (Mar. 26) 1943.
91. HORSFALL, F. L.: Primary Atypical Pneumonia, New York State J. Med. **46:** 1810–1814 (Aug. 15) 1946.
92. HORSFALL, F. L., AND CURNEN, E. C.: Studies on Pneumonia Virus of Mice. PVM, J. Exper. Med. **83:** 43–64 (Jan.) 1946.
93. HOWARD, M., BLAKE, F. G., AND TATLOCK, H.: Feline Pneumonia Following Inoculation with Human Nose and Throat Washings. Federation Proceed. **4:** 147–148 (Mar.) 1945.
94. MEIKLEJOHN, G., EATON, M. D., AND VANHERICK, W.: A Clinical Report on Cases of Primary Atypical Pneumonia Caused by a New Virus, J. Clin. Invest. **24:** 241–250 (Mar.) 1945.
95. MILLS, K. C., AND DOCHEZ, A. B.: Specific Agglutination of Murine Erythrocytes by a Pneumonitis Virus in Mice. Proc. Soc. Exp. Biol. & Med. **57:** 140–143 (Oct.) 1944.
96. ROSE, H. M., AND MOLLOY, E.: Observations Concerning the Etiology of Primary Atypical Pneumonia, Science **98:** 112–114 (July 30) 1943.
97. STOKES, J., REIMANN, H. A., AND SHAW, D. R.: A New Filtrable Agent Associated with Respiratory Infections. Abst. J. Bact. **38:** 242 (Aug.) 1939.
98. STOKES, J., KENNEY, G. S., AND SHAW, D. S.: A New Filtrable Virus Associated with Respiratory Infections, Trans. & Studies, Coll. Phys. Philadelphia, **6:** 329–333 (Feb.) 1939.
99. THOMAS, H. M.: Rôle of Alpha Hemolytic Streptococcus in Pneumonia. Bull. Johns Hopkins Hosp. **72:** 218–231 (Apr.) 1943.
100. THOMAS, L., AND OTHERS: Complement-Fixation with Dissimilar Antigens in Primary Atypical Pneumonia. Proc. Soc. Exp. Biol. & Med. **52:** 121–125 (Feb.) 1943.
101. THOMAS, L., AND OTHERS: Studies in Primary Atypical Pneumonia. II. Observations Concerning the Relationship of a Non-Hemolytic Streptococcus to the Disease. J. Clin. Invest. **24:** 227–240 (Mar.) 1945.
102. VANCE, D. H., SCOTT, T., AND MASON, T.: Inability to Pass Primary Atypical Pneumonia to Human Volunteers. Science **98:** 412, 1943.
103. WEIR, J. M., AND HORSFALL, F. L.: The Recovery from Patients with Acute Pneumonitis of a Virus Causing Pneumonia in the Mongoose. J. Exper. Med. **72:** 595 (Nov.) 1940.

GENERAL REFERENCES

104. ADAMS, A. B., AND OTHERS: Primary Atypical Pneumonia. Brit. Med. J. **1:** 227–231 (Feb. 16) 1946.
105. ADAMS, J. M.: Primary Virus Pneumonitis with Cytoplasmic Inclusion Bodies. J. A. M. A. **116:** 925–933 (Mar. 8) 1941. ADAMS, J. M., AND OTHERS: Primary Pneumonitis.

J Ped 20. 405–420 (Apr) 1942 ADAMS, J M Third Epidemic of Primary Virus Pneumonitis Among Infants in Minnesota Journal-Lancet 65. 129–194 (May) 1945

106 ALLEN, E V , AND BAIRD, L W Pneumonia in the Army New Orleans M & S J 96: 177–184 (Nov) 1943

107 ALLEN, W H Acute Pneumonitis Ann Int Med 10. 441–446, 1936

108 ALLISON, S T Penicillin in Primary Atypical Pneumonia Report of 28 Cases U S Nav Med Bull 45: 930–932 (Nov) 1945

109 ANDRUS, P M Silent Bronchopneumonia Canadian M A J 47: 339–342 (Oct) 1942

110 APPLEBAUM, A A , AND HURFORD, C E Primary Atypical Pneumonia Michigan State M S J 43: 979–989 (Nov) 1944

110a APPLEBAUM, I L , AND SHRAGER, J Pneumonitis Associated with Malaria Arch Int Med 74: 155–162 (Sept) 1944

111 ARNASMITH, T M Influenzal Pneumonia—A Clinical Report, with Special Reference to Diagnosis U S Nav Med Bull 28: 769–783, 1930

112 BAHLER, A M Some Differential Points in Diagnosis of Atypical Pneumonia of Probable Virus Origin New York State J Med 43: 315–317 (Feb 15) 1943

113 BAYLIN, G J , DUBIN, I N , AND GORNEL, W G Effect of Roentgen Therapy on Experimental Virus Pneumonias, I Feline Virus Pneumonia Am J Roent 55: 473–477 (Apr) 1946

114 BECKER, R P Pneumonia Complicating Mild Respiratory Infections Canadian M A J 48: 324–332 (Apr) 1943

115 BEJARANO, J F R Epidemiology of Acute Nontuberculous, Nondestructive Pneumonias in Argentine Army Rev San Mil Buenos Aires 43: 581–618 (May) 1944

116 BERNHARD, R W , AND CHAPMAN, D W Primary Atypical Pneumonia Indiana State M A J 37: 584–588 (Nov) 1944

117 BERRYHILL, W R , AND OTHERS Primary Atypical Pneumonia, Etiology Unknown North Carolina M J 4: 421–430 (Oct) 1943

118 BOCK, A V Clinical Observations, Complications, and Treatment of Acute Upper Respiratory Tract Infections Ann Int Med 12: 317–322, 1938

119 BLADES, B , AND DUGAN, D J Pseudo-Bronchiectasis Following Atypical Pneumonia Bull U S Army M Dept No 70 60–70 (Nov) 1943

120 BOWEN, A Acute Influenza Pneumonitis Amer J Roentgenol 34: 168–174, 1935

121 BRESLOW, L Epidemic of Acute Respiratory Disease Associated with Atypical Pneumonia J Clin Invest 24: 775–779 (Nov) 1945

122 BRETHAUER, E A , AND THOMPSON, R T Observations of Atypical Pneumonia of the Influenzal Virus Type Ann Int Med 20: 884–889 (June) 1944

123 CAMPBELL, E T Primary Atypical Pneumonia and Malaria War Med 3: 249–255 (Mar) 1943

124 CAMPBELL, T A , AND OTHERS Primary Atypical Pneumonia 200 Cases at Fort Eustis, Virginia J A M A 122: 723–729 (July 10) 1943

125 CASS, J W Question of Influenzal and Atypical Pneumonia New England J Med 214: 187–193 (Jan 30) 1936

126 CHAPMAN, D W Primary Atypical Pneumonia Report of 47 Cases Iowa State M S J 34: 391–394 (Sept) 1944

127 COLE, R I Acute Pulmonary Infections, Do Lamar Lectures 1927–28, Williams & Wilkins Co , 1928

128 COLLEN, G W Virus Pneumonia Permanente Found M Bull 1: 45–50 (Oct) 1943

129 Commission on Acute Respiratory Diseases Association of Acute Pulmonary Lesions with Infection of the Throat Ann Int Med 25: 473–487 (Sept) 1946

129a Commission on Acute Respiratory Diseases Association of Pneumonia with Erythema Multiforme Exudativum, Arch Int Med 78. 687–710 (Dec) 1946 (b) STANYON, J H , AND WARNER, W P Mucosal Respiratory Syndrome, Canad M A J 53. 127–134 (Nov) 1946

130 CONLIN, F Atypical Pneumonia of Unknown Etiology So Called "Virus Pneumonia" Nebraska M J 28. 47–50 (Feb) 1943

131. Contratto, A. W.: So-called "Atypical Pneumonia" Among College Students. New England J. Med. 229: 229–238, 1943.
132. Cooch, J. W.: Primary Atypical Pneumonia: Report of 25 Cases with Discussion of Pathogenesis. Kansas M. S. J. 46: 1–6 (Jan.) 1945.
133. Correll, H. L., and Cowan, I. I.: Primary Atypical Pneumonia; Analysis of the Therapeutic Results in 155 Cases. U. S. Nav. Bull. 41: 980, 1943.
134. Cunningham, T. D.: Virus Pneumonia. Rocky Mountain Med. J. 39: 764–766 (Nov.) 1942.
135. Curnen, E. C.: "Virus Pneumonias." J. Ped. 29: 309–315 (Sept.) 1946.
136. Curtzwiler, F. C., and Moore, B. E.: Primary Atypical Pneumonia of Unknown Etiology. Radiol. 40: 347–350 (Apr.) 1943.
137. Cutts, F. B., and Lawson, H. A.: Primary Atypical Pneumonia, Etiology Unknown. Rhode Island M. J. 27: 11–12 (Jan.) 1944.
138. Daniels, W. B.: Bronchopneumonia of Unknown Etiology in a Girl's School. Amer. J. Med. Sci. 203: 263–276, 1942.
139. Davenport, L. F.: Atypical Pneumonias. Bull. New England M. Center 4: 17 (Feb.) 1942.
140. Dingle, J. H., and Finland, M.: Virus Pneumonias. II. Primary Atypical Pneumonia of Unknown Etiology. New England J. Med. 227: 378, 1942.
141. (a) Dingle, J. H., and others: Primary Atypical Pneumonia, Etiology Unknown. Am. J. Hyg. 39: 67–128 (Jan.), (b) 39: 197–268 (Mar.), and (c) 269–336 (May) 1944. (d) Dingle, J. H., and others: Primary Atypical Pneumonia, Etiology Unknown. War Med. 3: 223–248 (Mar.) 1943.
142. Dochez, A. R., Cole, R., and Libman, E.: Discussion of Reimann, Reference 240.
143. Dougherty, M. S.: Primary Atypical Pneumonia of Unknown Cause. Georgia M. A. J. 33: 76–78 (Mar.) 1944.
144. Drew, W. R. M., Samuel, E., and Bull, M.: Primary Atypical Pneumonia. Lancet 1: 761–765 (June 19) 1943.
145. Duggan, L. B., and Powers, W. L.: Acute Respiratory Infection Resembling So-Called Acute Pneumonitis; Report of 40 Cases. J. Lab. and Clin. Med. 28: 524–530, 1943.
146. Ebert, R. V., and Stead, E. A.: Circulatory Failure in Acute Infections. J. Clin. Invest. 20: 671–679 (Nov.) 1941.
147. Elliott, J. F., and McRae, D. L.: Virus Pneumonia. J. Canadian M. Serv. 2: 162–174 (Jan.) 1945.
148. Emerson, K., and others: Chloride Metabolism and Plasma Amino Acid Levels in Primary Atypical Pneumonia. J. Clin. Invest. 22: 695–697 (Sept.) 1943.
149. Englehardt, H. T., and Wilen, C. J. W.: Virus Pneumonia. South. Med. J. 35: 973–975 (Nov.) 1942.
150. Erickson, G. C., and Van Ravenswaay, A. C.: Management of Primary Atypical Pneumonia Based on Controlled Study of 645 Cases seen at Station Hospital. South. Med. J. 37: 326–330 (June) 1944.
151. Favour, C. B.: Infections Associated with Epidemic of Primary Interstitial Pneumonia. New England J. Med. 230: 537–541 (May 4) 1944.
152. Field, H.: Acute Respiratory Infections, Including Virus Pneumonias. West Virginia M. J. 40: 69–73 (Mar.) 1944.
153. Finklestein, D., and Klainer, M. J.: Pericarditis Associated with Primary Atypical Pneumonia. Amer. Heart J. 28: 385–394 (Sept.) 1944.
154. Fleming, S., Lindick, E. W., and Evans, I. H.: "Primary Atypical Pneumonia," An Epidemic Associated with Malaria. Brit. M. J. 1: 689–693 (May 19) 1945.
155. Flexner, M., and Garson, M. L.: Virus Pneumonia: Treatment with Convalescent Blood. Kentucky M. J. 41: 5–13 (Jan.) 1943.
155a. Francis, T.: Virus Pneumonia. Canadian J. Pub. Health 35: 49–54 (Feb.) 1944.
156. Fredd, H.: Atypical Pneumonias. New York State J. Med. 41: 34–39 (Jan. 1) 1941.

. Fulghum, C. B.: Virus Pneumonia. J. M. A. Georgia 32: 317-7 (Oct.) 1943.
. Fuller, C. C., and Quinlan, J. W.: Acute Pneumonitis and Pericarditis, New England J. Med. 229: 399-401 (Sept. 2) 1943.
. Gallagher, J. R.: Bronchopneumonia in Adolescents. Yale J. Biol. and Med. 7: 23-40, 1934.
. Gallagher, J. R.: Acute Pneumonitis. A Report of 87 Cases Among Adolescents. Yale J. Biol. and Med. 13: 663-678, 1941.
. Gallagher, J. R.: Acute Pneumonitis. Yale J. Biol. and Med. 13: 769-781, 1941.
2. Gill, A. M.: Pneumonitis. Brit. Med. J. 1: 504-507, 1938.
3. Glendy, E. R., Beasen, S. B., and Hawkins, W. D.: Primary Atypical Pneumonia of Unknown Cause with Unusual Manifestations and Complications. Arch. Int. Med. 75: 30-38 (Jan.) 1945.
4. Golden, A.: Pathologic Anatomy of "Atypical Pneumonia," Etiology Undetermined, Acute Interstitial Pneumonitis. Arch. Path. 38: 187-202 (Oct.) 1944.
5. Goodman, S.: Atypical Pneumonia. J. Oklahoma M. A. 35: 504-507 (Dec.) 1942.
6. Goodpasture, E. W., and others: Virus Pneumonia of Infants Secondary to Epidemic Infections. Am. J. Dis. Child. 57: 997-1007 (May) 1939.
7. Goodrich, B. E., and Branford, H. A.: The Recognition of Virus Type Pneumonia. Am. J. Med. Sci. 204: 163-179 (Aug.) 1942.
8. Green, D. M., and Eldridge, F. G.: Primary Atypical Pneumonia, Etiology Unknown. Mil. Surg. 91: 508-516 (Nov.) 1942.
9. Grossman, J.: Some Observations on Primary Atypical Pneumonia. Arch. Int. Med. 76: 328-331 (Nov.-Dec.) 1945.
10. Gsell, O., and Engel, M.: Pneumonia Resistant to Sulfonamide Drugs. Schweiz. Med. Wchnsch. 72: 35-37 (Jan. 10) 1942.
11. Gundersen, S.: Primary Atypical Pneumonia of Unknown Etiology. New England J. Med. 231: 697-700 (Nov. 23) 1944.
12. Guthrie, M. B., and Reesen, R.: Primary Atypical Pneumonia: Analysis of 140 Cases. Florida M. A. J. 31: 101-103 (Sept.) 1944.
13. Haemio, E., and Hayden, W.: Influenza-like Epidemic with High Incidence of Pulmonary Infiltrates (Virus Pneumonia) in an Infantry Battalion. Schweizer. Med. Wchnsch. 72: 1113-1118 (Oct. 10) 1942.
14. Hafkenschiel, J. H.: Atypical Pneumonia at an Air Base in India During Winter of 1944. Mil. Surg. 97: 377-379 (Nov.) 1945.
15. Haight, W. L., and Thalinger, J. H.: Primary Atypical Pneumonia; Etiology Unknown. U. S. Nav. Med. Bull., 41: 980-1000, 1943.
16. Haines, H. F., and Forcey, C. M.: Primary Atypical Pneumonia as Seen in the Tropics. Med. Clin. N. America 28: 1490-1496 (Nov.) 1944.
17. Hamburger, W. W.: Variations of Primary Atypical Pneumonia. Cincinnati J. Med. 27: 292-312 (May) 1946.
18. Harvey, R. M.: Rib Fractures in Atypical Pneumonia. Am. J. Roent. 52: 487-493 (Nov.) 1944.
19. Hein, G. E.: (Discussion) Lancet 1: 431-432 (Apr. 3) 1943. Brown, J. W., and others, Proc. Roy. Soc. Med. 36: 385, 1943.
20. Herxheimer, H. G. F., and McMillan, A. J.: Atypical "Influenza Pneumonia" at a School. Brit. M. J. 2: 513 (Oct. 31) 1942.
21. Higley, C. S., Warren, H. A., and Harrison R. S.: Complications of Primary Atypical Pneumonia. Bull. U. S. Army Med. Dept. No. 83, 67-72 (Dec.) 1944.
22. Hobby, A. W.: Lobar, Broncho- and Atypical Pneumonia: Study of 500 Cases. U. S. Nav. Med. Bull. 43: 438-449 (Sept.) 1944.
22a. Helmes, J. M.: Neurological Complications in Atypical Pneumonia, Brit. M. J. 1: 218-220 (Feb. 8) 1947.
23. Hoagland, F. L.: Primary Atypical Pneumonia. N. Y. State J. Med. 46: [illegible] (Aug. 15) 1946.

184. Hufford, C. E., and Applebaum, A. A.: Atypical Pneumonia of Probable Virus Origin. Radiol. 40: 351 (Apr.) 1943.
185. Ingleby, H.: Encephalitis Complicating Virus Pneumonia. Arch. Path. 37: 359–366, 1944.
186. Iverson, H. A.: An Epidemic of Acute Respiratory Disease Associated with Atypical Pneumonia. Bull. Johns Hopkins Hosp. 72: 89–100 (Feb.) 1943.
187. Jensen, C. R.: Non-suppurative Post-streptococcic (Rheumatic) Pneumonitis. Pathologic Anatomy and Clinical Differentiation from Primary Atypical Pneumonia. Arch. Int. Med. 77: 235–253 (Mar.) 1946.
188. Kanin, H. N.: Virus Pneumonia. Illinois M. J. 83: 41–43 (Jan.) 1943.
189. Karpel, S., Waggoner, I. M., and McCown, O. S.: Primary Atypical Pneumonia; Clinical Analysis of 500 Cases. Ann. Int. Med. 22: 408–417 (Mar.) 1945.
190. Kasich, M., and Cohen, I. S.: Primary Atypical Pneumonia. J. M. Soc. New Jersey, 40: 358–362 (Sept.) 1943.
191. Kay, E. B.: Ulcerative Tracheobronchitis Following Atypical Pneumonia. Report of Cases. Arch. Int. Med. 76: 93–101 (Aug.) 1945.
192. Kelley, W. H.: Primary Atypical Pneumonia. South Carolina Med. Asso. J. 39: 119–121 (May) 1943.
193. Kneeland, Y., and Smetana, H. F.: Current Bronchopneumonia of Unusual Character and Undetermined Etiology. Bull. Johns Hopkins Hosp. 67: 229–267 (Oct.) 1940.
194. Kotin, E. H.: Probable Genetic Susceptibility to Viral Pneumonia, Ann. Int. Med. (To Be Published) 1947.
195. Kruger, A. L., and others: Primary Atypical Pneumonia Simulating Infiltrative Pulmonary Tuberculosis. Dis. Chest 10: 171–179 (May–June) 1944.
196. Langille, J. A.: Acute Pneumonitis or Virus Pneumonia. Nova Scotia M. Bull. 21: 333–337 (Nov.) 1942.
197. Langmuir, A. D.: Epidemiology of Atypical Pneumonia and Acute Respiratory Disease at Fort Bragg, North Carolina. Am. J. Pub. Health 34: 335–346 (Apr.) 1944.
198. Leake, W. H., and Blatchford, F. W.: Primary Atypical Pneumonia. U. S. Nav. Med. Bull. 41: 1624–1626 (Nov.) 1943.
199. Lembcke, P. A., and Young, L. E.: Incidence of Respiratory Infections Following Attack by Primary Atypical Pneumonia is Unchanged. Amer. J. Med. Sci. 210: 762–764 (Dec.) 1945.
200. Levin, S. L.: Primary Atypical Pneumonia, Etiology Unknown: Report of Thirty-Five Cases. Bull. Vet. Admin. 20: 122–127 (Oct.) 1943.
201. Longcope, W. T.: Bronchopneumonia of Unknown Etiology (Variety X) Bull. Johns Hopkins Hosp. 67: 268–305 (Oct.) 1940.
202. Lusk, F. B., and Lewis, E. K.: Atypical Pneumonia of Unknown Etiology. Dis. Chest 10: 19–40 (Jan.–Feb.) 1944.
203. Lusk, F. B., and Lewis, E. K.: Recognition of Atypical Pneumonia. Illinois Med. J. 86: 263–268 (Nov.) 1944.
204. Lyght, C. E., and Cole, L. R.: Pneumonia as It Affects Young Adults: Three Hundred Consecutive Cases at the University of Wisconsin. Ann. Int. Med. 14: 2246–2254 (June) 1941.
205. Markham, J.: Acute Pneumonitis: An Atypical Bronchopneumonia of Virus Origin. Canadian M. A. J. 47: 133–139 (Aug.) 1942.
206. Maxfield, J. R.: Atypical Pneumonia with Leukopenia. Texas State J. Med. 35: 340–346, 1939.
207. Maxwell, J.: Pneumonitis, Lancet 2: 239–241, 1938.
208. McCoy, W. C.: Primary Atypical Pneumonia. A Report of 420 Cases with One Fatality. South. Med. J. 39: 696–705 (Sept.) 1946.
209. McDonald, J. B., and Ehrenpreis, B.: The Clinical and Roentgenological Manifestation of Primary Atypical Pneumonia, Etiology Unknown. Ann. Int. Med. 24: 153–169 (Feb.) 1946.

210. McKinlay, C. A., and Cowan, D. W.: Acute Respiratory Infections Including Lobar Pneumonia and Atypical Pneumonia in a Young Adult Group. Journal-Lancet 61: 125-133, 1941.
211. McKinlay, C. A., Lange, E. H., and Boehrer, J. J.: Pneumonia Associated with Rheumatic Endocarditis. Journal-Lancet 62: 75-79 (Mar.) 1942.
212. McLeod, C.: Primary Atypical Pneumonia. Med. Clin. N. Amer. 27: 670-686 (May) 1943.
213. McNaught, J. B.: Virus Pneumonia: A Review of the Pathology. California & West. Med. 59: 220-223 (Oct.) 1943.
214. Meakins, J. F.: Primary Atypical Pneumonia of Unknown Etiology. Canadian M. A. J. 48: 333-336 (Apr.) 1943.
215. Meyer, O., and Thewlis, E. W.: The Leukocyte Count in Primary Atypical Pneumonia of Unknown Etiology. Ann. Int. Med. 21: 977-982, (Dec.) 1944.
216. Miller, F. N., and Hayes, M.: Bronchopneumonia of Mild Severity at University of Oregon. Northwest. Med. 38: 12-14, 1939.
217. Moore, G. B., Jr., Tannenbaum, A. J., and Smaha, T. G.: Atypical Pneumonia in an Army Camp. War Med. 2: 615-622, 1942.
218. Moore, N. S., Wightman, H. B., and Showacne, E. C.: Primary Atypical Pneumonia, I: A Statistical Report of 196 Cases. New York State J. Med. 44: 869-872, 1944.
219. Moss, J.: Some Features of "Virus Pneumonias." North Carolina M. J. 3: 27-30 (Jan.) 1942.
220. Murray, M. E.: Atypical Bronchopneumonia of Unknown Etiology. Possibly Due to a Filtrable Virus. New England J. Med. 222: 565-573, 1940.
221. Napier, L. E.; Chaudhuri, R. N., and Rai Chaudhuri, M. N.: Pneumonitis, Indian M. Gaz. 77: 399-401 (July) 1942.
222. Needles, R. J., and Gilbert, P. D.: Primary Atypical Pneumonia; Report of 125 Cases, with Autopsy Observations in One Fatal Case. Arch. Int. Med. 73: 113-122, 1944.
223. Norris, J. C.; McLaughlin, R. F., and Williams, F. S.: Primary Atypical Pneumonia Virus Type. A Brief Review—Necropsy Case Presentation. Mil. Sur. 98 299-304 (Apr.) 1946.
224. Official Statement. Primary Atypical Pneumonia, Etiology Unknown. War Med. 2: 339, 1942.
225. Offutt, V. D.: Diagnosis and Treatment of Primary Atypical Pneumonia. South. Med. & Surg. 106: 5-6 (Jan.) 1944.
226. Oppenheim, A.: Roentgen Therapy of "Virus" Pneumonia. Am. J. Roentgen. 49: 635-638 (May) 1943.
227. Owen, C. A.: Primary Atypical Pneumonia. An Analysis of Seven Hundred and Thirty-Eight Cases Occurring During 1942, at Scott Field, Illinois. Arch. Int. Med. 73: 217-231 (Mar.) 1944.
228. Page, S. G., and Tittle, C. R.: Primary Atypical Pneumonia. Virginia Med. Monthly 71: 305-308 (June) 1944.
229. Painton, J. F.; Hicks, A. M., and Hartman, S.: Clinical Analysis of Primary Atypical Pneumonia with a Discussion of Electrocardiographic Findings. Ann. Int. Med. 28: 775-807 (May) 1946.
230. Peña, V.: Primary Atypical Pneumonia. Gac. méd de Caracas. 61: 137-138, 1944.
231. Penrond, H., and Wright, M. A.: Fatal Case of Atypical Pneumonia with Encephalitis. Brit. Med. J. 2: 63-65 (July 13) 1943.
232. Pinkerton, H.; Smiley, W. L., and Anderson, W. A. D.: Giant Cell Pneumonia with Inclusions. Am. J. Path. 21: 1-15 (Jan.) 1945.
233. Plummer, N., and Ensworth, H. K.: Primary Atypical Pneumonia in General Hospitals and in Private Practice. Bull. N. Y. Acad. Med. 20: 292-308 (May) 1944.
234. Pratt, L. A.: Primary Atypical Pneumonia, Etiology Unknown; Bronchoscopic Examination. Am. J. Hyg. 39: 302-307 (May) 1944.

235. Prilla, E.: Primary Atypical Pneumonia, Etiology Unknown. Illinois M. J. 83: 183–187 (Mar.) 1943.
236. Racker, E.; Rose, S. P., and Turner, A. O.: Pneumococcic Pneumonia Resembling Primary Atypical Pneumonia. Am. J. Med. Sci. 209: 496–502 (Apr.) 1945.
237. Rainey, W. G., and Burbidge, J. R.: Acute Pneumonitis or Atypical Pneumonia. Journal-Lancet 59: 101–104, 1939.
238. Ramsay, H., and Scadding, J. G.: Benign Broncho-pulmonary Inflammations Associated with Transient Radiographic Shadows. Quart. J. Med. 32: 79–95, 1939.
239. Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia. A Disease Entity Probably Caused by a Filtrable Virus. J. A. M. A. 111: 2377–2384, 1938.
240. Reimann, H. A., and Stokes, J.: An Epidemic Infection of the Respiratory Tract in 1938–39: A Newly Recognized Entity. Tr. A. Am. Phys. 54: 123–125, 1939.
241. Reimann, H. A., and Havens, W. P.: An Epidemic Disease of the Respiratory Tract. Arch. Int. Med. 65: 138–150, 1940.
242. Reimann, H. A.; Havens, W. P., and Price, A. H.: Etiology of Atypical ("Virus") Pneumonias. Arch. Int. Med. 70: 513–522 (Oct.) 1942.
243. Reimann, H. A.: Viral Pneumonia. Bull. N. Y. Acad. Med. 19: 177–182 (Mar.) 1943.
244. Reimann, H. A.: Primary Atypical Pneumonia of Unknown Cause. "Virus" or Viral Pneumonias: Case Report of a Similar Disease Without Pneumonia. J. Michigan State M. Soc. 43: 147–150 (Feb.) 1944.
245. Reimann, H. A.: Atypical Pneumonia, Viral Pneumonia or Viroid Pneumonia? J. A. M. A. 127: 543 (Mar. 3) 1945.
246. Reimann, H. A.: Viral Infections of the Respiratory Tract, Their Treatment and Prevention. J. A. M. A. 132: 487–493 (Nov. 2) 1946.
246a. Rhoads, P. S.: The Probable Incidence and Clinical Features of "Virus" Pneumonia Radiol. 40: 327–338 (Apr.) 1943.
247. Rich, C.: Classification of So-Called Atypical Pneumonia. Canadian M. A. J. 53: 265–274 (Sept.) 1945.
248. Riven, S. S., and Stern, E. A.: Virus Pneumonia. South. Med. J. 35: 976–980 (Nov.) 1942.
249. Robertson, A. F.: Report of One Epidemic of an Acute Respiratory Infection with Pneumonitis. Virginia Med. Monthly 69: 342–343 (Oct.) 1942.
250. Rothenberg, R. C.: Atypical (Virus) Pneumonia. A Case with Autopsy Report. Cincinnati J. Med. 24: 152–154 (June) 1943.
251. Saphir, O.: Pathological Changes in So-Called Atypical Pneumonia. Radiol. 40: 339–343 (Apr.) 1943.
252. Scadding, J. G.: Disseminated Focal Pneumonia. Brit. Med. J. 2: 956–959, 1937.
253. Sachs, J.: Recent Advances in Diagnosis and Treatment of Virus and Atypical Pneumonia. New York State J. M. 44: 485–487 (Mar. 1) 1944.
254. Schmitz, R. C.: Primary Atypical Pneumonia (Virus Pneumonia). Wisconsin M. J. 43: 228–230 (Feb.) 1944.
255. Schmitz, R. C.: Primary Atypical Pneumonia of Unknown Cause. Arch. Int. Med. 75: 222–232, 1945.
256. Scott, W. G., and Jones, H. L.: Acute Pneumonitis. Am. J. Roentgenol. 50: 444–452 (Oct.) 1943.
257. Sheppe, W. M., and others: Meningomyelitis: A Complication of Primary Atypical Pneumonia. J. A. M. A. 122: 1245–1246 (Aug. 28) 1943.
258. Shibley, G. S.; Mills, K. C., and Dochez, A. R.: J. A. M. A. 95: 1553, 1930; Webster, L. T., and Clow, A. D.: J. Exper. Med. 55: 445, 1932; Kneeland, G., and Dawes, C. F.: J. Exper. Med. 55: 735, 1932; Smillie, W. G.: Trans. Asso. Am. Phys. 56: 128, 1941.
259. Short, J. J.: Penicillin in Treatment of Primary Atypical Pneumonia: 9 Cases. U. S. Nav. Med. Bull. 43: 974–980 (Nov.) 1944.

260. Sienknecht, E. C.: Virus Pneumonia. Kentucky State M. J. 44: 217–218 (July) 1946.
261. Sison, A. B. M.; Jimenez, V., and Herrera, F.: Virus Pneumonia in the Philippine Islands, To be published.
262. Smiley, D. R.; Showacre, E. E.; Lee, W. F., and Ferris, H. W.: Acute Interstitial Pneumonitis, a New Disease Entity. J. A. M. A. 112: 1901–1904, 1939.
263. Smith, J. H.: Virus Pneumonia in Contrast with Other Types, Virginia Med. Month. 70: 353–357 (July) 1943.
264. Smith, R. H.: Primary Atypical Pneumonia, Etiology Unknown. The Average Clinical Picture Based on Thirty-seven Original Cases. Ann. Int. Med. 20: 890–902 (June) 1944.
265. Solomon, E. M.: Human Sorum Treatment of Atypical Pneumonia. J. Lab. & Clin. Med. 29: 493–499 (May) 1944.
266. Spink, W. W.: Atypical Pneumonia. Minn. Med. 26: 337–339 (Apr.) 1943.
267. Sprunt, D. H.; Martin, D. S., and Williams, J. E.: Interstitial Bronchopneumonia. I. Similarity of a Toxin Pneumonia to that Produced by the Viruses. J. Exper. Med. 62: 73–83, 1935.
268. Stewart, W. C.: Virus Pneumonia. West Virginia Med. J. 39: 248–251 (July) 1943.
269. Suttenfield, F. D.: Primary Atypical Pneumonia (Virus Pneumonia). Mil. Surg. 93: 360–364, 1943.
270. Tansey, W. A.; Culver, P. J., and First, T. F.: Primary Atypical Pneumonia: Statistical Analysis. New Jersey Med. Soc. J. 42: 288–293 (Sept.) 1945.
271. Theodos, P. A., and Zwickel, R. E.: Clinical Aspects of Primary Atypical Pneumonia. Med. Bull. North African Theater of Oper. 2: 104–109 (Nov.) 1944.
272. The Virus Pneumonias, Principles of Bacteriology and Immunology, Topley and Wilson, Vol. 3, Ed. 3, 1946, p. 1876.
273. Thompson, J. L.: Primary Atypical Pneumonia. Report Based on Study of 250 Cases. Med. Ann. Dist. Columbia 12: 171–174 (May) 1943.
274. Tumulty, P. A.: Atypical Pneumonia: A Diagnostic Problem in the Tropics, Bull. Johns Hopkins Hosp. 75: 269–302 (Nov.) 1944.
275. Vance, D. H.; Scott, T., and Mason, H. C.: Inability to Pass Primary Atypical Pneumonia to Human Volunteers. Science 98: 412–413 (Nov. 5) 1943.
276. Van Ravenswaay, and others: Clinical Aspects of Primary Atypical Pneumonia. J. A. M. A. 124: 1–6, 1944.
276a. Wall, J. S.: Interstitial Bronchopneumonia in Children. South Med. J. 30: 201–206 (Feb.) 1937.
277. Wechsler, H. F.; Rosenblum, A. H., and Silk, C. T.: Infectious Mononucleosis: Report of an Epidemic in an Army Post, Part I, Ann. Int. Med. 25: 113–133 (July) 1946.
278. Whitely, J. H.; Bernstein, A., and Goldman, M.: Primary Atypical Pneumonia—A Report of Twenty-five Cases. Mil. Surg. 91: 499–502 (Nov.) 1942.
278a. Wilner, P. R.: Virus Pneumonia: Differentiation from Pulmonary Tuberculosis. Med. Ann. Dist. Columbia 15: 385–390 (Aug.) 1946.
279. Wolff, L.: Acute Pericarditis with Special Reference to Heart Size. New England J. Med. 229: 423–431, 1943.
280. Wolff, H. J.: Virus Pneumonia. A Resumé and a Therapeutic Suggestion. Minn. Med. 28: 43–46 (Jan.) 1945.
281. Wolfson, S. A.: Value of Sedimentation Rate Determinations in Management of Primary Atypical Pneumonia, Etiology Unknown. Mil. Surg. 94: 370–372 (June) 1944.
281a. Wolventon, B. F.: Primary Atypical Pneumonia. J. Iowa State M. Soc. 36: 485–487 (Nov.) 1946.
282. Yaskalka, J. S.: Atypical Pneumonia Simulating Pulmonary Tuberculosis. Amer. Rev. Tuberc. 49: 408–413 (May) 1944.

235. Prilla, E.: Primary Atypical Pneumonia, Etiology Unknown. Illinois M. J. **83**: 183–187 (Mar.) 1943.
236. Racker, E.; Rose, S. P., and Turner, A. O.: Pneumococcic Pneumonia Resembling Primary Atypical Pneumonia. Am. J. Med. Sci. **209**: 496–502 (Apr.) 1945.
237. Rainey, W. G., and Burbidge, J. R.: Acute Pneumonitis or Atypical Pneumonia. Journal-Lancet **59**: 101–104, 1939.
238. Ramsay, H., and Scadding, J. G.: Benign Broncho-pulmonary Inflammations Associated with Transient Radiographic Shadows. Quart. J. Med. **32**: 79–95, 1939.
239. Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia. A Disease Entity Probably Caused by a Filtrable Virus. J. A. M. A. **111**: 2377–2384, 1938.
240. Reimann, H. A., and Stokes, J.: An Epidemic Infection of the Respiratory Tract in 1938–39: A Newly Recognized Entity. Tr. A. Am. Phys. **54**: 123–125, 1939.
241. Reimann, H. A., and Havens, W. P.: An Epidemic Disease of the Respiratory Tract. Arch. Int. Med. **65**: 138–150, 1940.
242. Reimann, H. A.; Havens, W. P., and Price, A. H.: Etiology of Atypical ("Virus") Pneumonias. Arch. Int. Med. **70**: 513–522 (Oct.) 1942.
243. Reimann, H. A.: Viral Pneumonia. Bull. N. Y. Acad. Med. **19**: 177–182 (Mar.) 1943.
244. Reimann, H. A.: Primary Atypical Pneumonia of Unknown Cause. "Virus" or Viral Pneumonias: Case Report of a Similar Disease Without Pneumonia. J. Michigan State M. Soc. **43**: 147–150 (Feb.) 1944.
245. Reimann, H. A.: Atypical Pneumonia, Viral Pneumonia or Viroid Pneumonia? J. A. M. A. **127**: 543 (Mar. 3) 1945.
246. Reimann, H. A.: Viral Infections of the Respiratory Tract, Their Treatment and Prevention. J. A. M. A. **132**: 487–493 (Nov. 2) 1946.
246a. Rhoads, P. S.: The Probable Incidence and Clinical Features of "Virus" Pneumonia Radiol. **40**: 327–338 (Apr.) 1943.
247. Rich, C.: Classification of So-Called Atypical Pneumonia. Canadian M. A. J. **53**: 265–274 (Sept.) 1945.
248. Riven, S. S., and Stern, E. A.: Virus Pneumonia. South. Med. J. **35**: 976–980 (Nov.) 1942.
249. Robertson, A. F.: Report of One Epidemic of an Acute Respiratory Infection with Pneumonitis. Virginia Med. Monthly **69**: 342–343 (Oct.) 1942.
250. Rothenberg, R. C.: Atypical (Virus) Pneumonia. A Case with Autopsy Report. Cincinnati J. Med. **24**: 152–154 (June) 1943.
251. Saphir, O.: Pathological Changes in So-Called Atypical Pneumonia. Radiol. **40**: 339–343 (Apr.) 1943.
252. Scadding, J. G.: Disseminated Focal Pneumonia. Brit. Med. J. **2**: 956–959, 1937.
253. Sachs, J.: Recent Advances in Diagnosis and Treatment of Virus and Atypical Pneumonia. New York State J. M. **44**: 485–487 (Mar. 1) 1944.
254. Schmitz, R. C.: Primary Atypical Pneumonia (Virus Pneumonia). Wisconsin M. J. **43**: 228–230 (Feb.) 1944.
255. Schmitz, R. C.: Primary Atypical Pneumonia of Unknown Cause. Arch. Int. Med. **75**: 222–232, 1945.
256. Scott, W. G., and Jones, H. L.: Acute Pneumonitis. Am. J. Roentgenol. **50**: 444–452 (Oct.) 1943.
257. Sheppe, W. M., and others: Meningomyelitis: A Complication of Primary Atypical Pneumonia. J. A. M. A. **122**: 1245–1246 (Aug. 28) 1943.
258. Shibley, G. S.; Mills, K. C., and Dochez, A. R.: J. A. M. A. **95**: 1553, 1930; Webster, L. T., and Clow, A. D.: J. Exper. Med. **55**: 445, 1932; Kneeland, G., and Dawes, C. F.: J. Exper. Med. **55**: 735, 1932; Smillie, W. G.: Trans. Asso. Am. Phys. **56**: 128, 1941.
259. Short, J. J.: Penicillin in Treatment of Primary Atypical Pneumonia: 9 Cases. U. S. Nav. Med. Bull. **43**: 974–980 (Nov.) 1944.

260. Sienknecht, E. C.: Virus Pneumonia. Kentucky State M. J. 44: 217–218 (July) 1946.
261. Sison, A. B. M.; Jimenez, V., and Herrera, F.: Virus Pneumonia in the Philippine Islands, To be published.
262. Smiley, D. R.; Showacre, E. E.; Lee, W. F., and Ferris, H. W.: Acute Interstitial Pneumonitis, a New Disease Entity. J. A. M. A. 112: 1901–1904, 1939.
263. Smith, J. H.: Virus Pneumonia in Contrast with Other Types, Virginia Med. Month. 70: 353–357 (July) 1943.
264. Smith, R. H.: Primary Atypical Pneumonia, Etiology Unknown. The Average Clinical Picture Based on Thirty-seven Original Cases. Ann. Int. Med. 20: 890–902 (June) 1944.
265. Solomon, E. M.: Human Serum Treatment of Atypical Pneumonia. J. Lab. & Clin. Med. 29: 493–499 (May) 1944.
266. Spink, W. W.: Atypical Pneumonia. Minn. Med. 26: 337–339 (Apr.) 1943.
267. Spaunt, D. H.; Martin, D. S., and Williams, J. E.: Interstitial Bronchopneumonia. I. Similarity of a Toxin Pneumonia to that Produced by the Viruses. J. Exper. Med. 62: 73–83, 1935.
268. Stewart, W. C.: Virus Pneumonia. West Virginia Med. J. 39: 248–251 (July) 1943.
269. Suttenfield, F. D.: Primary Atypical Pneumonia (Virus Pneumonia). Mil. Surg. 93: 360–364, 1943.
270. Tansey, W. A.; Culver, P. J., and First, T. F.: Primary Atypical Pneumonia: Statistical Analysis. New Jersey Med. Soc. J. 42: 288–293 (Sept.) 1945.
271. Theodos, P. A., and Zwickel, R. E.: Clinical Aspects of Primary Atypical Pneumonia. Med. Bull. North African Theater of Oper. 2: 104–109 (Nov.) 1944.
272. The Virus Pneumonias, Principles of Bacteriology and Immunology, Topley and Wilson, Vol. 3, Ed. 3, 1946, p. 1876.
273. Thompson, J. L.: Primary Atypical Pneumonia. Report Based on Study of 250 Cases. *Med. Ann. Dist. Columbia 12: 171–174 (May) 1943.*
274. Tumulty, P. A.: Atypical Pneumonia: A Diagnostic Problem in the Tropics, Bull. Johns Hopkins Hosp. 75: 269–302 (Nov.) 1944.
275. Vance, D. H.; Scott, T., and Mason, H. C.: Inability to Pass Primary Atypical Pneumonia to Human Volunteers. Science 98: 412–413 (Nov. 5) 1943.
276. Van Ravenswaay, and others: Clinical Aspects of Primary Atypical Pneumonia. J. A. M. A. 124: 1–6, 1944.
276a. Wall, J. S.: Interstitial Bronchopneumonia in Children. South Med. J. 30: 201–206 (Feb.) 1937.
277. Wechsler, H. F.; Rosenblum, A. H., and Silk, C. T.: Infectious Mononucleosis: Report of an Epidemic in an Army Post, Part I, Ann. Int. Med. 25: 113–133 (July) 1946.
278. Whitely, J. H.; Bernstein, A., and Goldman, M.: Primary Atypical Pneumonia—A Report of Twenty-five Cases. Mil. Surg. 91: 499–502 (Nov.) 1942.
278a. Wilner, P. R.: Virus Pneumonia: Differentiation from Pulmonary Tuberculosis. Med. Ann. Dist. Columbia 15: 385–390 (Aug.) 1946.
279. Wolff, L.: Acute Pericarditis with Special Reference to Heart Size. New England J. Med. 229: 423–431, 1943.
280. Wolff, H. J.: Virus Pneumonia. A Resumé and a Therapeutic Suggestion. Minn. Med. 28: 43–46 (Jan.) 1945.
281. Wolfson, S. A.: Value of Sedimentation Rate Determinations in Management of Primary Atypical Pneumonia, Etiology Unknown. Mil. Surg. 94: 370–372 (June) 1944.
281a. Wolventon, B. F.: Primary Atypical Pneumonia. J. Iowa State M. Soc. 36: 185–187 (Nov.) 1946.
282. Yaskalka, J. S.: Atypical Pneumonia Simulating Pulmonary Tuberculosis. Amer. Rev. Tuberc. 49: 408–413 (May) 1944.

235. Prilla, E.: Primary Atypical Pneumonia, Etiology Unknown. Illinois M. J. **83**: 183–187 (Mar.) 1943.
236. Racker, E.; Rose, S. P., and Turner, A. O.: Pneumococcic Pneumonia Resembling Primary Atypical Pneumonia. Am. J. Med. Sci. **209**: 496–502 (Apr.) 1945.
237. Rainey, W. G., and Burbidge, J. R.: Acute Pneumonitis or Atypical Pneumonia. Journal-Lancet **59**: 101–104, 1939.
238. Ramsay, H., and Scadding, J. G.: Benign Broncho-pulmonary Inflammations Associated with Transient Radiographic Shadows. Quart. J. Med. **32**: 79–95, 1939.
239. Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia. A Disease Entity Probably Caused by a Filtrable Virus. J. A. M. A. **111**: 2377–2384, 1938.
240. Reimann, H. A., and Stokes, J.: An Epidemic Infection of the Respiratory Tract in 1938–39: A Newly Recognized Entity. Tr. A. Am. Phys. **54**: 123–125, 1939.
241. Reimann, H. A., and Havens, W. P.: An Epidemic Disease of the Respiratory Tract. Arch. Int. Med. **65**: 138–150, 1940.
242. Reimann, H. A.; Havens, W. P., and Price, A. H.: Etiology of Atypical ("Virus") Pneumonias. Arch. Int. Med. **70**: 513–522 (Oct.) 1942.
243. Reimann, H. A.: Viral Pneumonia. Bull. N. Y. Acad. Med. **19**: 177–182 (Mar.) 1943.
244. Reimann, H. A.: Primary Atypical Pneumonia of Unknown Cause. "Virus" or Viral Pneumonias: Case Report of a Similar Disease Without Pneumonia. J. Michigan State M. Soc. **43**: 147–150 (Feb.) 1944.
245. Reimann, H. A.: Atypical Pneumonia, Viral Pneumonia or Viroid Pneumonia? J. A. M. A. **127**: 543 (Mar. 3) 1945.
246. Reimann, H. A.: Viral Infections of the Respiratory Tract, Their Treatment and Prevention. J. A. M. A. **132**: 487–493 (Nov. 2) 1946.
246a. Rhoads, P. S.: The Probable Incidence and Clinical Features of "Virus" Pneumonia Radiol. **40**: 327–338 (Apr.) 1943.
247. Rich, C.: Classification of So-Called Atypical Pneumonia. Canadian M. A. J. **53**: 265–274 (Sept.) 1945.
248. Riven, S. S., and Stern, E. A.: Virus Pneumonia. South. Med. J. **35**: 976–980 (Nov.) 1942.
249. Robertson, A. F.: Report of One Epidemic of an Acute Respiratory Infection with Pneumonitis. Virginia Med. Monthly **69**: 342–343 (Oct.) 1942.
250. Rothenberg, R. C.: Atypical (Virus) Pneumonia. A Case with Autopsy Report. Cincinnati J. Med. **24**: 152–154 (June) 1943.
251. Saphir, O.: Pathological Changes in So-Called Atypical Pneumonia. Radiol. **40**: 339–343 (Apr.) 1943.
252. Scadding, J. G.: Disseminated Focal Pneumonia. Brit. Med. J. **2**: 956–959, 1937.
253. Sachs, J.: Recent Advances in Diagnosis and Treatment of Virus and Atypical Pneumonia. New York State J. M. **44**: 485–487 (Mar. 1) 1944.
254. Schmitz, R. C.: Primary Atypical Pneumonia (Virus Pneumonia). Wisconsin M. J. **43**: 228–230 (Feb.) 1944.
255. Schmitz, R. C.: Primary Atypical Pneumonia of Unknown Cause. Arch. Int. Med. **75**: 222–232, 1945.
256. Scott, W. G., and Jones, H. L.: Acute Pneumonitis. Am. J. Roentgenol. **50**: 444–452 (Oct.) 1943.
257. Sheppe, W. M., and others: Meningomyelitis: A Complication of Primary Atypical Pneumonia. J. A. M. A. **122**: 1245–1246 (Aug. 28) 1943.
258. Shibley, G. S.; Mills, K. C., and Dochez, A. R.: J. A. M. A. **95**: 1553, 1930; Webster, L. T., and Clow, A. D.: J. Exper. Med. **55**: 445, 1932; Kneeland, G., and Dawes, C. F.: J. Exper. Med. **55**: 735, 1932; Smillie, W. G.: Trans. Asso. Am. Phys. **56**: 128, 1941.
259. Short, J. J.: Penicillin in Treatment of Primary Atypical Pneumonia: 9 Cases. U. S. Nav. Med. Bull. **43**: 974–980 (Nov.) 1944.

260. Sienknecht, E. C.: Virus Pneumonia. Kentucky State M. J. 44: 217–218 (July) 1946.
261. Sison, A. B. M.; Jiménez, V., and Herrera, F.: Virus Pneumonia in the Philippine Islands, To be published.
262. Smiley, D. R.; Showache, E. E.; Lee, W. F., and Ferris, H. W.: Acute Interstitial Pneumonitis, a New Disease Entity. J. A. M. A. 112: 1901–1904, 1939.
263. Smith, J. H.: Virus Pneumonia in Contrast with Other Types, Virginia Med. Month. 70: 353–357 (July) 1943.
264. Smith, R. H.: Primary Atypical Pneumonia, Etiology Unknown. The Average Clinical Picture Based on Thirty-seven Original Cases. Ann. Int. Med. 20: 890–902 (June) 1944.
265. Solomon, E. M.: Human Serum Treatment of Atypical Pneumonia. J. Lab. & Clin. Med. 29: 493–499 (May) 1944.
266. Spink, W. W.: Atypical Pneumonia. Minn. Med. 26: 337–339 (Apr.) 1943.
267. Sprunt, D. H.; Martin, D. S., and Williams, J. E.: Interstitial Bronchopneumonia. I. Similarity of a Toxin Pneumonia to that Produced by the Viruses. J. Exper. Med. 62: 73–83, 1935.
268. Stewart, W. C.: Virus Pneumonia. West Virginia Med. J. 39: 248–251 (July) 1943.
269. Suttenfield, F. D.: Primary Atypical Pneumonia (Virus Pneumonia). Mil. Surg. 93: 360–364, 1943.
270. Tansey, W. A.; Culver, P. J., and First, T. F.: Primary Atypical Pneumonia: Statistical Analysis. New Jersey Med. Soc. J. 42: 288–293 (Sept.) 1945.
271. Theodos, P. A., and Zwickel, R. E.: Clinical Aspects of Primary Atypical Pneumonia. Med. Bull. North African Theater of Oper. 2: 101–109 (Nov.) 1944.
272. The Virus Pneumonias, Principles of Bacteriology and Immunology, Topley and Wilson, Vol. 3, Ed. 3, 1946, p. 1876.
273. Thompson, J. L.: Primary Atypical Pneumonia. Report Based on Study of 250 Cases. Med. Ann. Dist. Columbia 12: 171–174 (May) 1943.
274. Tumulty, P. A.: Atypical Pneumonia: A Diagnostic Problem in the Tropics, Bull. Johns Hopkins Hosp. 75: 269–302 (Nov.) 1944.
275. Vance, D. H.; Scott, T., and Mason, H. C.: Inability to Pass Primary Atypical Pneumonia to Human Volunteers. Science 98: 412–413 (Nov. 5) 1943.
276. Van Ravenswaay, and others: Clinical Aspects of Primary Atypical Pneumonia. J. A. M. A. 124: 1–6, 1944.
276a. Wall, J. S.: Interstitial Bronchopneumonia in Children. South Med. J. 30: 201–206 (Feb.) 1937.
277. Wechsler, H. F.; Rosenblum, A. H., and Silk, C. T.: Infectious Mononucleosis: Report of an Epidemic in an Army Post, Part I, Ann. Int. Med. 25: 113–133 (July) 1946.
278. Whitely, J. H.; Bernstein, A., and Goldman, M.: Primary Atypical Pneumonia—A Report of Twenty-five Cases. Mil. Surg. 91: 499–502 (Nov.) 1942.
278a. Wilner, P. R.: Virus Pneumonia: Differentiation from Pulmonary Tuberculosis. Med. Ann. Dist. Columbia 15: 385–390 (Aug.) 1946.
279. Wolff, L.: Acute Pericarditis with Special Reference to Heart Size. New England J. Med. 229: 423–431, 1943.
280. Wolff, H. J.: Virus Pneumonia. A Resumé and a Therapeutic Suggestion. Minn. Med. 28: 43–46 (Jan.) 1945.
281. Wolfson, S. A.: Value of Sedimentation Rate Determinations in Management of Primary Atypical Pneumonia, Etiology Unknown. Mil. Surg. 94: 370–372 (June) 1944.
281a. Wolverton, B. F.: Primary Atypical Pneumonia. J. Iowa State M. Soc. 36: 485–487 (Nov.) 1946.
282. Yaskalka, J. S.: Atypical Pneumonia Simulating Pulmonary Tuberculosis. Amer. Rev. Tuberc. 49: 408–413 (May) 1944.

283. YASKALKA, J. S.: Primary Atypical Pneumonia, Etiology Unknown: Clinical Study of 96 Cases. New Jersey M. Soc. J. 41: 188–193 (May) 1944.
284. YOUNG, L. E.; STOREY, M., AND REDMOND, A. J.: Clinical and Epidemiological Features of an Outbreak of Primary Atypical Pneumonia of Unknown Etiology Among Hospital and Medical School Personnel. Am. J. Med. Sci. 206: 756–762 (Dec.) 1943.
284a. LIEGLER, J. E., AND OTHERS: Diagnosis of Acute Respiratory Tract Infections, Am. J. Med. Sci. 213: 268–281 (March) 1947.

REFERENCES ON COLD HEMAGGLUTININS

285. Commission on Acute Respiratory Diseases. Cold Hemagglutinins in Primary Atypical Pneumonia and Other Respiratory Infections. Am. J. Med. Sci. 208: 742–750 (Dec.) 1944.
286. DAMESHEK, W.: Cold Agglutinins in Acute Hemolytic Reactions in Association with Sulfonamide Medication and Injections. J. A. M. A. 123: 77–80 (Sept. 11) 1943.
287. FAVOUR, C. B.: Autohemagglutinins—"Cold Agglutinins." J. Clin. Invest. 23: 891–897 (Nov.) 1944.
288. FETTERMAN, G. H.; Moran, T. J., AND HESS, W. R.: The Cold Agglutinin Test. U. S. Nav. Med. Bull. 43: 1128–1136, 1944.
289. FINLAND, M., AND OTHERS: Cold Agglutinins: Occurrence of Cold Isohemagglutinins in Various Conditions. J. Clin. Invest. 24: 451–457 (July) 1945.
290. FINLAND, M., AND OTHERS: Cold Agglutinins: II: Cold Isohemagglutinins in Primary Atypical Pneumonia of Unknown Etiology with a Note on the Occurrence of Hemolytic Anemia in these Cases. J. Clin. Invest. 24: 458–473, 1945.
291. FINLAND, M., AND OTHERS: Cold Agglutinins: VI. Agglutinins for an Indifferent Streptococcus in Primary Atypical Pneumonia and in Other Conditions and the Relation to Cold Isohemagglutinins. J. Clin. Invest. 24: 497–502, 1945.
292. FLORMAN, A. L., AND WEISS, A. B.: Serologic Reactions in Primary Atypical Pneumonia. J. Lab. Clin. Med. 30: 902–909 (Nov.) 1945.
293. GINSBERG, H. S.: Acute Hemolytic Anemia in Primary Atypical Pneumonia Associated with High Titer of Cold Agglutinins: Report of Case. New England J. Med. 234: 826–828 (June 20) 1946.
294. HEINTZELMAN, J. H. L., AND SELIGMAN, A. W.: Evaluation of Cold Agglutination Test in Primary Atypical Pneumonia. U. S. Nav. Med. Bull. 43: 433–437 (Sept.) 1944.
295. HELWIG, F. C., AND FREIS, E. D.: Cold Autohemagglutins Following Atypical Pneumonia Producing the Clinical Picture of Acrocyanosis. J. A. M. A. 123: 626–628 (Nov. 6) 1943.
296. HORSTMAN, D. M., AND TATLOCK, H.: Cold Agglutinins: A Diagnostic Aid in Certain Types of Primary Atypical Pneumonia. J. A. M. A. 122: 369–370 (June 5) 1943.
297. HUMPHREY, A. A.: Cold Hemagglutination Test in Diagnosis of Primary Atypical Pneumonia. U. S. Nav. Med. Bull. 43: 1117–1127, 1944.
298. MEIKLEJOHN, G.: The Cold Agglutinin Test in the Diagnosis of Primary Atypical Pneumonia. Proc. Soc. Exp. Biol. & Med. 54: 181 (Nov.) 1943.
299. MCCARTY, A. C., AND INFIELD, G. L.: Poor Diagnostic Value of Cold Agglutinins in Primary Atypical Pneumonia. Kentucky M. J. 42: 317–318 (Oct.) 1944.
300. MCNEILL, C.: The Relationshipof Cold Agglutinins to the Course of Primary Atypical Pneumonia. Am. J. Med. Sci. 209: 48–54 (Jan.) 1945.
301. PAREKH, J. G.: Phenomenon of Autoagglutination in Man after Sulfapyridine. Indian M. Gaz. 78: 527–531 (Nov.) 1943.
302. PETERSON, O. L.; HAM, T. H., AND FINLAND, M.: Cold Agglutinins (Autohemagglutinins) in Primary Atypical Pneumonia. Science 97: 167 (Feb. 12) 1943.
303. PETERSON, O. L., AND OTHERS: Cold Agglutinins; 1, Occurrence of Cold Isohemagglutinins in Various Conditions. J. Clin. Invest. 24: 451–457 (July) 1945.

301. Platt, W. R., and Ward, C. S.: Cold Isohemagglutinins: Their Association with Hemolytic Anemia and Multiple Thrombosis in Primary Atypical Pneumonia. Amer. J. Clin. Path. 15: 202-209 (May) 1945.
305. Rich, C. B.; Rae, M. V., and McGoey, C. J.: Cold Agglutinins and the Pneumonias. Canad. M. A. J. 51: 239-240 (Sept.) 1944.
306. Shone, S., and Passmore, R.: Pneumonitis Associated with Autohemagglutination. Lancet 2: 445-446 (Oct. 9) 1943.
307. Springarn, C. L., and Jones, J. P.: Cold Hemagglutination in Primary Atypical Pneumonia and Other Common Infections. Arch. Int. Med. 76: 75-87 (Aug.) 1945.
308. Streeter, G. A.; Farmer, T. W., and Hayes, G. S.: Cold Hemagglutination in Primary Atypical Pneumonia. Bull. Johns Hopkins Hosp. 75: 60-65 (July) 1944.
309. Turner, J. C.: Development of Cold Agglutinins in Atypical Pneumonia. Nature 151: 419 (Apr. 10) 1943.
310. Turner, J. C., and others: Relation of Cold Agglutinins to Atypical Pneumonia Lancet 1: 765-767 (June 19) 1943.

REFERENCES ON ROENTGENOLOGIC STUDIES

311. Bacuman, A. L., Sara, N. O., and Mantz, H. E.: Pleuritic Involvement Associated with Primary Atypical Pneumonia. Amer. J. Roentgen. 53: 244-258 (Mar.) 1945.
312. Bernhard, R. W.: Roentgen Aspect of Atypical or Virus Pneumonia. Iowa State M. S. J. 34: 395-402 (Sept.) 1944.
313. Chysler, W. E.: The Roentgenographic Manifestations of Atypical Pneumonia of Unknown Etiology. Am. J. Roentgenol. 51: 280-291, 1944.
313a. Chysler, W. E.: Primary Atypical Pneumonia: Disease of Segmental Distribution, ibid. 56: 321-336 (Sept.) 1946.
314. Grimm, H. W., and Denton, J.: Atypical Pneumonia with Roentgen and Pathologic Findings. Radiol. 44: 151-157 (Feb.) 1945.
315. Guzman, M.: Primary Atypical Pneumonia. Roentgenographic Study of 108 Cases in Puerto Rico. Bol. A. M. Puerto Rico. 36: 163-169 (Apr.) 1944.
316. Harvey, R. M.: Rib Fractures in Atypical Pneumonia, Am. J. Roentg. 52: 487-493 (Nov.) 1944.
317. Kennedy, J. A.: Pulmonary Complications of the Common Cold and Sinusitis. Finding in Mass Radiography. Lancet 1: 769-771 (June 19) 1943.
318. Kornblum, K., and Reimann, H. A.: The Roentgenological Aspects of an Epidemic of Acute Respiratory Tract Infection. Amer. Jour. Roentgenol. 44: 333, 1940.
319. Levene, G., and Sterman, I.: Roentgen Study of Primary Atypical Virus Pneumonia. Radiol. 42: 446-457 (May) 1944.
320. Lewis, E. K., and Lusk, F. B.: Roentgen Diagnosis of Primary Atypical Pneumonia. Radiol. 42: 425-434 (May) 1944.
321. McCarthy, P. V.: Primary Atypical Pneumonia of Unknown Etiology. Radiol. 40: 344 (April) 1943.
322. Seeds, A. E., and Mazer, M. L.: Virus Pneumonia; Roentgenographic Characterization of Recent Virus Pneumonitis with Bronchopneumonia. Am. J. Roentg. 49: 30-38, 1943.
323. Snowacre, E. C.; Wightman, H. B., and Moore, N. S.: Primary Atypical Pneumonia, II. Observations of Radiographic Patterns. New York State J. Med. 44: 872-879, 1944.
324. Stein, G. H., and Kresky, P. J.: Comparative Roentgen Study of Primary Atypical Pneumonia and Bacterial Pneumonia. Radiol. 42: 435-445 (May) 1944.
325. Weber, H. M.: Atypical Pneumonia; Peculiar Forms. Am. J. M. [illegible] (May) 1944.

KALA AZAR IN AMERICAN MILITARY PERSONNEL

Report of 30 Cases

MAJOR HARRY MOST,[1] M.C. and CAPTAIN PAUL H. LAVIETES,[2] M.C.

From the Tropical Disease Section, Moore General Hospital, Swannanoa, North Carolina

TABLE OF CONTENTS

CLINICAL

Introduction

Leishmaniasis fortunately did not constitute a serious or major military problem in World War II, despite the fact that a relatively large number of troops were stationed in highly endemic areas in the Mediterranean littoral, India, and China. Kala-azar occurred in military personnel from North Africa, Sicily, southern Italy, the Riviera and India, and it is estimated that 50 to 75 cases occurred in the army during the War. A small number of cases of kala-azar have developed in this country in military personnel who had previously served in endemic areas, and a few cases have been recognized in veterans after their separation from military service. It is not anticipated that many new cases will be recognized in this country in troops or veterans who have served in endemic areas.

Early and continued hospitalization and transfer of military patients to specialized treatment centers in this country made it possible to study the entire clinical course of the disease in many patients. Prolonged observation in a non-endemic area provided an excellent opportunity to evaluate the relative efficiency of various drugs, and to study in detail certain clinical pathological features of kala-azar not heretofore possible to study in endemic areas.

[1] Present address: 477 First Ave N. Y. C.

[2] Present address: 340 Whitney Ave New Haven, Conn.

Cases of kala-azar in this country before the war were rare and occurred in several instances in Indain merchant seamen (1, 2) or individuals previously residents of India, (3) China, (4) or Italy (2). Medical officers had little to no prior experience with kala-azar. This frequently resulted in delay in diagnosis and in inadequate or ineffective treatment. In some instances in this country individual cases were retained for definitive treatment and several reports of one or more cases have been submitted for publication (5). Thirty cases of suspected or proven kala-azar were received at Moore General Hospital, a tropical disease center, for diagnosis, initial treatment, retreatment, or observation. The authors' personal experience with these 30 cases will constitute the major portion of this report although reference will be made to other cases presenting unusual clinical problems.

General Considerations

(a) *Age and color:* 13 patients were 21–25 years of age, 12 were 26–30, 2 were 31–35, and 3 were from 36 to 40 years of age. 21 patients were white and 9 were colored.

(b) *Geographic origin of infection:* Fifteen (15) cases originated in India and 15 in the Mediterranean Theater, i.e. North Africa, Sicily, and southern Italy. We could not establish exactly where in the Mediterranean littoral the patients acquired the infection because all the cases from that theater with one exception had spent sufficient time in North Africa and Italy or North Africa, Italy and Sicily prior to the onset of the symptoms to have become infected in any or all of these endemic areas. One patient who was stationed in the vicinity of Paris spent one week on furlough in Nice and returned to Paris. Three weeks after leaving Nice he developed symptoms which were later proven to be due to kala-azar. In this case it is reasonably certain the disease was acquired in the vicinity of Nice.

(c) *Occupation:* The branches of service of the patients were as follows: Engineers 6, Army Air Forces ground crews 9, Quartermaster 8, Ordnance 2, Signal Corps 1, and Clerical 2. An officer attached to an air forces headquarters in India and an officer who was an infantry platoon commander in India are included in this series.

(d) *Possible source of infection:* Several species of *Phlebotomus* have been established as vectors responsible for the transmission of leishmaniasis. Our patients had no definite knowledge of having been bitten by sandflies though all stated they had been bitten by mosquitoes and other "insects and bugs". This is not unusual since the *Phlebotomus* is a minute fly only 1.5 to 2.5 mm. in length. The bite may cause a considerable local irritation but this can easily be attributed to other more readily visible arthropods.

Kala-azar occurs mostly in native villages and frequently it is a household infection. In this connection, it is of interest that one of our patients, an air air corps officer shared an apartment in Calcutta with two other officers. Two of the three occupants of this house developed proven kala-azar. Three of our patients were from the same company quartered at an air base on the outskirts

of Calcutta. Six patients stated that they had occupied native huts in a village recently vacated. One patient who was a truck driver slept repeatedly in a stable on the outskirts of a village. Five additional patients were truck drivers who travelled back and forth at night along the coast of North Africa and on many occasions found it necessary to sleep in their trucks in towns or villages. In the majority of our patients, therefore, ample opportunity for infection occurred by virtue of close contact at night with native villages or huts. In some cases, however, no history of residence in native villages or huts could be obtained.

(e) *Incubation period:* The incubation period in kala-azar is not definitely known and apparently varies considerably. Instances have been reported in which it has been as short as 2 weeks and as long as 18 months. In one of our cases we are fairly certain the incubation period was 3 weeks because the patient became ill three weeks after spending a week at Nice. This man had been on duty only in England and Paris before his short visit in the vicinity of Nice. In two of our cases the incubation period based on the interval between the last possible exposure in an endemic area and the development of the clinical disease in this country was at least 2 months. The longest possible incubation period representing the interval between arrival in an endemic area and the onset of symptoms was 33 months. One case in a veteran has recently been called to our attention (6) in which the incubation period was at least 19 months after the last possible exposure in an endemic area. This man was taken prisoner in Italy after prior service in North Africa and Sicily and removed to Germany in February 1944. He remained in Germany until his liberation and return to the United States where he was discharged from the army in August 1945. Symptoms developed insidiously during the next two months and he was hospitalized December 1945. The last possible exposure was in Italy during the first 10 days in February 1944. The shortest possible incubation period in this case would be from when he arrived in Germany until he became sick in this country, an interval of 19 months. This case emphasizes the importance of considering kala-azar in sick veterans who have clinical and laboratory findings described later in this paper even though they have left an endemic area a relatively long time ago.

Clinical Aspects at Onset

The onset of kala-azar as stated in texts of tropical medicine and papers dealing with disease is usually described as being "insidious or acute". The most striking clinical feature of the onset in our series of cases was its abruptness, being manifested by chills and high fever in the majority of patients. The essential features at onset will be described briefly below.

(a) *Fever:* In 29 or 96% of our patients the first symptom was fever associated with a chill of sufficient severity to warrant their seeking medical attention at a dispensary or hospital. From the standpoint of continuity of study of the disease in our patients the onset by chill and fever was fortunate in that it insured prompt hospitalization and resulted in continuous observation until the correct

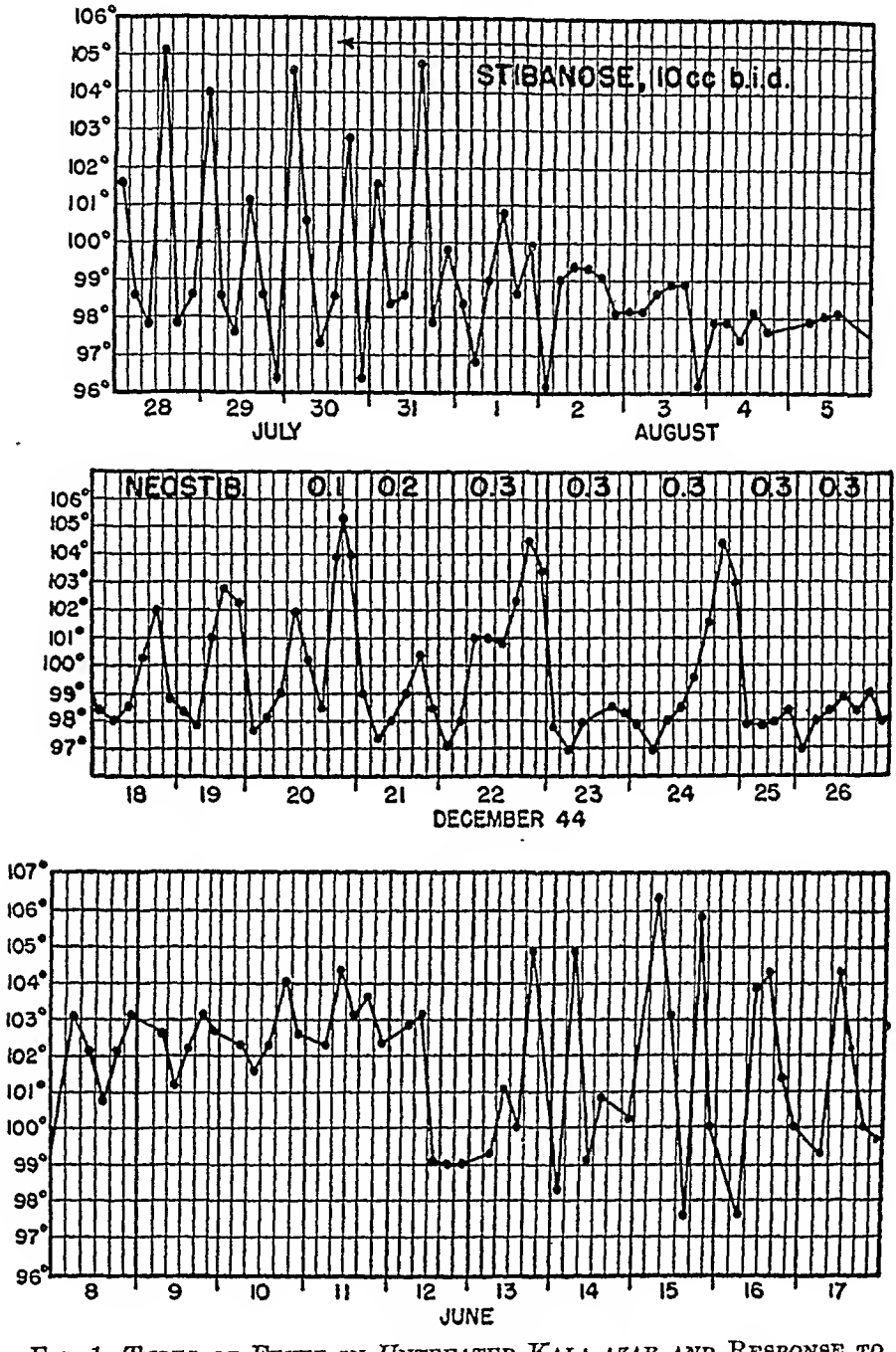


FIG. 1. TYPES OF FEVER IN UNTREATED KALA-AZAR AND RESPONSE TO SPECIFIC THERAPY

(a) Daily intermittent fever before treatment. Note double daily peaks. This type of fever was present in this patient for almost 3 months before treatment. Note prompt control of fever after institution of specific therapy (200 cc. stibanose). No relapse occurred during 6 month's observation.

(b) Note control of fever in this case within 6 days after institution of specific treatment (neostibosan 5.0 Gms.). Prior to treatment 2 rises in temperature (101° to 105°) occurred daily for 4 months. The tertian periodicity which occurred during treatment may also occur in untreated patients and simulate vivax malaria.

(c) Period of sustained fever simulating typhoid. Note characteristic double peaks later (Case 4).

(d) Spontaneous remission and exacerbation of fever without treatment simulating undulant fever (Case 6).

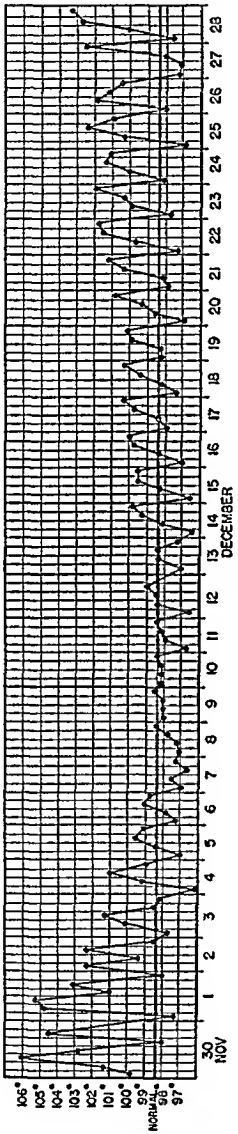

106°
105°
104°
103°
102°
101°
100°
99°
NORMAL
98°
97°
30
NOV
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
DECEMBER

FIG 1d

diagnosis was made and sufficiently long afterwards until the results of definitive specific therapy could be evaluated.

The fever in the acute phase of the disease was intermittent with one or two rises to 101° to 106° F. daily. Double peaks in the daily temperature curve have been emphasized as an important clinical feature which may be suggestive of kala-azar. This phenomenon was observed in 50% of our cases (fig. 1a.). While two or more peaks in the twenty-four hour temperature curve occur in other diseases the frequency with which it occurs in kala-azar is valuable in suggesting this disease as a possible diagnosis in a case of prolonged fever. The second rise in temperature may occur late at night and unless temperatures are taken every 2 or 3 hours during the day and night and charted graphically this phenomenon may be overlooked. In some patients the maximum rise in temperature occurs at approximately the same time every day and in a few patients there may be an exact tertian periodicity of chills and fever which recur every other day for a few days or for several weeks suggestive of *Plasmodium vivax* malaria (fig. 1b). Occasionally the temperature while intermittent may appear very irregular because of marked variation in the height of each maximum rise as well as the time of day or night of its occurrence. Intercurrent infection may alter the intermittent nature of the temperature and may result in periods of high sustained fever unless the new infection itself also produces intermittent fever. This assumes particular significance during treatment if a satisfactory response in respect to fever does not occur. A typhoid-like fever early in the disease occurs commonly in China but we have seen it only in one patient who had a sustained high fever for 10 days before it became intermittent (fig. 1c). Recurring febrile waves resembling the temperature pattern in brucellosis have been described in kala-azar particularly when its course is prolonged (fig. 1d). In our experience, this was not a prominent feature of the temperature curve even in patients who were febrile for as long as six months prior to diagnosis or treatment and was observed in only 4 patients. In the latter, there was a gradual subsidence in fever after 10 to 30 days of activity and the patients remained afebrile for 10 days to 6 weeks before fever occurred again. In only one patient in this series was fever entirely absent throughout the observed course of the disease.

Chills occurred initially or at some time in the disease in all but three patients. Many patients had one or more chills daily for weeks at a time. The nature of the chill did not differentiate it from the chill of other acute infections with the exception that the aching in the back and extremities and vomiting frequently seen in a paroxysm of malaria were not observed in the chill or febrile period in kala-azar. Profuse sweating followed the chill but if the patient were sponged and changed he seemed comfortable despite frequent periods of high fever.

(*b*) *Other symptoms at onset:* In the majority of patients there were surprisingly few complaints other than chills and fever. Although practically every patient had evident weight loss when first seen only two complained of weakness. The most common minor symptom was headache and occurred in eight individuals. Six patients complained of vague aches and pains and in two of these, the pains

were localized in the joints not accompanied by swelling or other objective joint changes. Only four patients had complaints referable to the gastrointestinal tract which consisted of periodic episodes of vomiting in three and diarrhea in one. Two patients noted enlargement of the abdomen which was found later to be due to splenomegaly and/or hepatomegaly and one man complained of pain in the left upper quadrant. One patient (Case 23) had recurrent epistaxis, another, bleeding from the gums. Bleeding phenomena were not noted in the other cases. A dry non-productive cough of several weeks duration not associated with physical signs or x-ray changes in the lungs occurred in one individual who gave this history when admitted to a hospital later because of chills and fever. One patient (Case 23) was hospitalized because of edema of the lower extremities and dyspnea. He was found to have hypertension, azotemia and hematuria. The diagnosis of kala-azar in this patient was an accidental finding as a result of a bone marrow examination which was done in an attempt to explain persistent leucopenia in a patient with acute diffuse glomerulonephritis. One patient (Case 27) was hospitalized because of jaundice, presumably infectious hepatitis, and in the course of his hospitalization other clinical and laboratory findings suggested kala-azar which was later established. And finally, one patient complained of painless progressive enlargement of the lymph nodes in the neck. In general, except for the chills and fever, the symptoms of onset in this disease were not striking and were not of great value in diagnosis.

(c) *Physical findings:* In spite of evident weight loss observed initially or later in practically every patient, it was noted by many observers who saw these patients early in the disease that they did not appear very ill. Comment was likewise made later when the intermittent febrile nature of the disease was established that despite prolonged periods of chills and high fever which might occur once or more often every day the patients did not appear "toxic", "septic", or "acutely ill". Similar statements concerning the general appearance of the patient in kala-azar may be found in most accounts of this disease. The skin showed no noteworthy changes in any of our patients. Except following a paroxysm or during a period of defervescence of fever when profuse sweating occurred, the skin was warm and dry. No pigmentary changes were observed and no purpura was seen. One patient had slight icterus of the skin, probably due to infectious hepatitis.

The eyes and fundi were normal in all our patients except for slight icterus of the sclerae in the one described above. The tongue as a rule was not coated and showed no gross evidence of severe nutritional deficiency. The gums in one patient were spongy, infected, receded from the teeth and bled very easily on manipulation. In this subject bleeding from the gums was a major complaint. The tonsils in one man were huge and they were removed prior to treatment but showed no *Leishmania* after smear, section, culture or hamster inoculation. In 7 patients cervical adenopathy was prominent. The lymph nodes were discrete, firm and not tender. Slight to moderate generalized lymphadenopathy was also present in these patients and played an important rôle clinically in the differential diagnosis because of co-existing splenomegaly and striking hematologic changes.

Lymph node biopsies were done on one or more occasions usually without suspicion of kala-azar in these 7 patients and *Leishmania* were demonstrated either initially or on review of the sections in 5 patients. No striking changes were observed in the heart or lungs. The blood pressures were normal or low normal in all but one patient who had hypertension associated with acute nephritis which may have been unrelated to kala-azar. The pulse averaged about 80 per minute except during fever when it ranged from 100 to 120 per minute. No disturbances in rhythm or the electrocardiogram were present prior to treatment. There were no remarkable findings in the lungs or chest x-rays except in three patients who had intercurrent pneumonia before or during treatment.

The most striking physical findings were in the abdomen and were related to enlargement of the liver or spleen or both. In 27 patients the spleen was found enlarged on the first examination, and in 3 additional patients the spleen enlarged later in the disease. In other words, 90% of the patients in this series had readily detectable splenomegaly at the clinical onset of the disease. 73% of the patients had enlargement of the liver on the first examination or subsequently in the course of the disease. No patient had hepatomegaly without coincident splenomegaly. In the patients having both organs enlarged the spleen was relatively much larger than the liver and varied in size from an edge readily palpable just below the costal margin to a grossly enlarged mass at or below the level of the umbilicus. Usually, the edge of the spleen was firm, smooth, and often tender. The speed with which the spleen enlarged was very striking in many cases and in one patient who had a barely palpable spleen on admission it was at the level of the umbilicus in one month. In several patients the spleen was well into the pelvis between the 3rd and 6th months of clinical activity. Frequently the spleen enlarged to the right so that the downward presentation was not striking. The liver at first was rarely more than 2 to 4 cm. below the costal margin and enlarged very slowly, never reaching the relatively huge size frequently attained by the spleen.

No abnormalities were noted in the extremities other than evidence of weight loss. There were no mental or neurological changes.

Differential Diagnosis

A variety of acute or chronic infectious and neoplastic diseases were suspected at onset or later in the evolution of this disease in our patients. Intermittent fever, splenomegaly, and pronounced hematologic changes were suggestive early in most cases of acute infection and later of some primary disease of the hemopoietic organs. This frequently resulted in intensive studies along these lines as well as numerous therapeutic trials with antimalarial drugs, sulfonamides, and penicillin. Occasionally the correct diagnosis was arrived at accidentally when lymph node or bone marrow material was examined in an effort to account for unexplained leucopenia, anemia, or lymphadenopathy. The diagnoses most frequently made at onset or later in the disease will be discussed briefly.

Malaria: In almost every case, malaria was suspected at onset. This is

view of the occurrence of chills and fever in patients in an area
nalaria. The low white count, mild anemia, moderate leucopenia,
egaly could all be accounted for on the basis of malaria although the
enomegaly frequently seen in these patients at onset has not been
often in vivax malaria in our troops. A few patients gave a prior
ived malaria and in several cases the temperature assumed a tertian
All these factors emphasize the importance of malaria in the
iagnosis of kala-azar at onset. Invariably repeated blood smear
for *Plasmodia* were negative. Therapeutic trials with quinine or
both frequently given in large amounts by mouth and parenterally
ble periods of time and often in repeated courses produced no
on the course of the fever.

This diagnosis was seriously considered in 5 patients from the
n Theater and in one from India. After varying periods of fever
patients had remissions lasting two to six weeks before becoming
However, repeated blood cultures were sterile and numerous
utination tests were negative. In brucellosis there are usually
ks in the daily temperature and the spleen rarely attains the huge
may reach in kala-azar. The white count is rarely depressed to
re degree in brucellosis at it may be in kala-azar.

Other acute or chronic infections: *Subacute bacterial endocarditis* was suspected in one patient. Repeatedly sterile blood cultures, lack of abnormal findings in the heart, absence of hematuria and petechiae, and the development of marked leucopenia caused an early abandonment of this diagnosis. *Miliary tuberculosis* was considered in a colored patient because of progressive weight loss, cough, intermittent fever, splenomegaly, and mild generalized lymphadenopathy. There were no pulmonary x-ray changes, however, after several months of continued intermittent fever. The onset of kala-azar in some patients who have only a low grade fever, cough and loss of weight is often suggestive of incipient pulmonary or other tuberculosis. *Dengue* was suspected in two patients. The "saddle back" fever of dengue may occur by chance early in kala-azar but the persistent fever after a week or more and absence of rash offer no difficulty in differentiating dengue from kala-azar after a short period of observation. *Typhoid fever* or *typhus* were considered for several weeks in five patients. In one of these, the temperature was very suggestive of typhoid during the first ten days. Blood, urine, or stool cultures and the Widal reaction are useful in establishing the diagnosis of typhoid. These are negative in kala-azar and of course no rose spots are seen in the latter. In areas where typhoid and kala-azar are both common, as in some parts of China, the onset of kala-azar is diagnosed as typhoid in approximately one-third of the cases. *Typhus* is a much more acute disease than kala-azar. In the latter, mental symptoms are noticeably absent. Vascular, hemorrhagic, and neurological complications are rare in kala-azar and the serological tests for typhus are negative. *Amoebiasis* was seriously considered in three cases. In one patient who had intermittent diarrhoea and cysts of *Endamoeba histolytica* in the stools amoebic hepatitis

was suspected. In another patient an amoebic abscess of the spleen was suspected and in the third patient an amoebic abscess of the liver was the presumptive diagnosis. These patients failed to improve following adequate therapy with emetine parenterally and other amebicidal drugs by mouth. Usually there is a leucocytosis in visceral amebiasis and response to emetine is usually dramatic. In amoebic abscess of the liver there is often fixation or alteration in the contour of the right diaphragm and occasionally a small amount of fluid is present in the right pleural sac. If facilities and antigen are available the complement fixation, if done, usually yields a strongly positive reaction. Fortunately, these patients were not subjected to laparotomy or aspiration. *Pneumonia* may complicate kala-azar particularly in poorly nourished natives. The diagnosis of pneumonia was made in two of our patients early in the course of kala-azar. One patient actually had pneumonia and with it leucocytosis. Despite adequate therapy with sulfonamides and penicillin, fever persisted and leucopenia developed. The pulmonary lesion resolved completely and it was obvious that pneumonia was not the underlying disease. The other patient had cough and fever on admission but persistent leucopenia, developing splenomegaly, and a negative chest x-ray suggested that pneumonia was not tenable as a diagnosis. It is of interest that intercurrent bacterial infections in the course of kala-azar frequently is associated with leucocytosis. The infection may overshadow the underlying disease and cause considerable delay in the diagnosis of kala-azar. Proper treatment of the intercurrent infection may result in clinical improvement but as a rule the temperature curve follows its usual kala-azar pattern and the white count falls to the leucopenic levels of that disease. *Infectious hepatitis* was diagnosed at onset in two patients. One patient complained of nausea and vomiting and was jaundiced on admission. He had an elevated serum bilirubin and may actually have had infectious hepatitis unless the jaundice was a part of his kala-azar. If so, this is an uncommon association. *Histoplasmosis* was suspected in one patient. The differentiation of this infection clinically from kala-azar may be extremely difficult for leucopenia, anemia, lymphadenopathy, splenomegaly and remittent fever also occur in histoplasmosis. In the latter, gastrointestinal, pulmonary or mucous membrane lesions may be present. The final differentiation depends on demonstrating organisms of *Histoplasma capsulatum* in smears, cultures, or sections of tissue. *Nephritis* of some form was suspected in two patients and in one of these with hematuria, edema, hypertension and azotemia an acute diffuse glomerulonephritis undoubtedly was present. While this may have been a purely coincidental condition in the course of kala-azar and the two may be related since their coexistence has been commented on in the literature of kala-azar (7) (22). In our patient the nephritis overshadowed the underlying kala-azar for some time and the latter diagnosis was made only accidentally when bone marrow was examined in an effort to explain persistent leucopenia and anemia. Proteinuria occurs commonly in kala-azar and in addition the cellular constituents in the urine may be increased considerably above normal values. Finally, the diagnosis of *Fever of Unknown Origin* (FUO) was the last diagnosis in nine patients when they were transferred to general hospitals overseas or this country after continued study and failure to establish a diagnosis.

Acute or chronic diseases primarily related to the hemopoietic organs: *Hodgkins Disease, acute aleukemic leukemia, aplastic anemia,* and *infectious mononeucleosis* were considered seriously in approximately 50% of our cases of kala-azar and in some patients one of these diagnoses was considered tenable for at least three months. Acute aleukemic leukemia was suspected because of the splenomegaly, slight generalized lymphadenopathy, fever, anemia, and marked leucopenia. However, in leukemia careful study of the peripheral blood will almost always reveal the presence of highly immature white cells even if only in small numbers. Gum hyperplasia and bleeding phenomena are common and the fever is rarely of the continued intermittent type seen in kala-azar. The bone marrow usually represents a one cell type appearance with a preponderance of undifferentiated cells and sections of lymph nodes are fairly characteristic of leukemia. In *Hodgkins* disease while there may be periods of continued high fever, the latter is not usually of the same daily intermittent type seen in kala-azar. The lymph nodes frequently become matted together and may assume huge proportions. Itching of the skin is common and is often associated with eosinophilia and leucocytosis although occasionally leucopenia is present. The histology of the lymph node as a rule establishes the diagnosis. It should be emphasized that progressive painless enlargement of lymph nodes without fever, splenomegaly or blood changes may occur in leishmaniasis. Cases of this kind have been reported from China and Brazil and more recently in 2 American soldiers (8). Such findings occurred in one case in the present series. The diagnosis is made by finding *leishmania donovani* in smears and sections of lymph nodes. Consideration must therefore be given to the possibility of the existence of kala-azar in patients presenting progressive cervical adenopathy and a history of residence in an area endemic for leishmaniasis. Aplastic anemia was suspected twice. In this disease there is fairly uniform depression of the formed blood elements. In kala-azar the reduction in the white count is disproportionate to the degree of anemia and although the platelets may be reduced in kala-azar they rarely reach the low levels seen in aplastic anemia. In the latter disease bleeding from mucous membranes and purpura are more common and more severe than in kala-azar. Fever is uncommon in aplastic anemia. Finally, in kala-azar the presence of reticulocytes and young white cells indicate continuous blood regeneration. In *infectious mononucleosis,* suspected in several of our patients because of lymphadenopathy, splenomegaly and relative lymphocytosis, abnormal lymphocytoid monocytes are present, the white count is usually elevated and the heterophile agglutination test is usually positive. These findings are not present in kala-azar. It is not intended as a result of this discussion to convey the impression that all febrile diseases associated with leucopenia, splenomegaly, hepatomegaly, and/or lymphadenopathy are kala-azar. However, this disease should be considered seriously in patients with the above findings who have been in leishmaniasis-endemic areas. Recently splenectomy was performed in a general hospital in this country on an Italian prisoner of war more than a year after his arrival in the United States (9). This patient had fever, leucopenia, anemia, hyperglobulinemia and splenomegaly. The spleen after removal weighed 1,660 Gms. and was found to contain large numbers of *Leishmania.*

Preoperatively a variety of hematologic, infectious (including kala-azar) and neoplastic diseases were considered. Bone marrow smears were negative when examined at the general hospital but *Leishmania* were reported from specimens submitted to the Army Institute of Pathology. Awareness of this disease should not interfere with other studies designed to establish other possible diagnoses but may materially shorten the interval from onset of clinical symptoms and signs to correct diagnosis. And, in the case of kala-azar, early diagnosis is important since adequate specific therapy is followed by dramatic cessation of activity of the disease and complete cure in the vast majority of patients.

Diagnosis

The diagnosis of kala-azar is established by the demonstration of *Leishmania donovani* in smears, sections, cultures or following hamster inoculation of material derived from spleen, liver, bone marrow, lymph nodes or blood. The relative abundance of parasites in these organs has been states to be in the above order. The results of various diagnostic procedures in 30 cases of kala-azar are summarized in table 1. In this series parasites were found in the peripheral blood in only one case in which the diagnosis was previously unsuspected.

Careful search of 8 smears at Moore General Hospital failed to reveal any *Leishmania*. In one series of 300 proved cases, positive smears were observed in only 3; while in another series of 23 cases, 9 positive smears were found (23).

Sternal marrow aspiration is a fairly simple and safe procedure which, in recent years, has been extensively resorted to in the study of various hematologic and related disorders. In 29 of our patients sternal puncture was performed on one or more occasions for diagnostic purposes and a total of 49 different punctures were done, all but 4 before admissions to Moore General Hospital. The diagnosis was established with one puncture in 14 cases, with a second puncture in 3 more, and with a third puncture in 4 more. This left the disease undiagnosed by one or more sternal marrow examinations in 8 of the 29 patients in whom this procedure was attempted. Of the 49 punctures, only 21 were positive. *Leishmania* were subsequently demonstrated in these patients in Moore General Hospital by initial splenic puncture without attempting sternal puncture. In each of 4 cases in which sternal puncture was done in Moore General Hospital, *Leishmania* were demonstrated by smear and culture. They appeared in relatively small number, however, in contrast to the many seen in splenic preparations. The average age of the disease (10 weeks) was similar in the patients from whom marrow smears were negative compared to those from whom positive results were obtained. In one patient a positive smear was obtained during the first week of the clinical disease. Success in finding *Leishmania* in bone marrow smears depends on familiarity with the morphology of the parasites, their abundance, the intensity of search, and whether marrow material rather than blood has been obtained. In one patient two different punctures were negative on smear but positive after culture on NNN medium. This emphasizes the desirability of resorting to culture if smears are negative. Cultures should not be discarded before a month since growth may occasionally be relatively slow.

Spleen puncture was performed in 18 patients and gave positive results in all. The diagnosis was established by lymph node biopsy in the one patient with a negative sternal puncture done overseas. Three specimens of positive

TABLE 1

Results of diagnostic procedures in 30 cases of proven kala-azar

CASE	BONE MARROW		SPLEEN		LYMPH NODE		BLOOD		OTHER
	Smear	Culture	Smear	Culture	Section	Smear	Smear	Culture	
1.	0 0 +		+	+					
2.	+								
3.	+		+	+			0	0	
4.	0 0 0		+	+			0	0	
5.	0 0 +								
6.	0	+	+	+			0	0	Skin 0; Tonsil 0
7.	0 0 +	0 + +	+	+					
8.	+				+				
9.			+	+					
10.	0		+	+			0	0	
11.	0 +		+	+	0 (+)		0	0	
12.	0 0 0				+	+			
13.	0 +		+	+	0 (+)		0	0	
14.	0 +		+	+			0	0	
15.	+								
16.	0		+	+					
17.	+		+	+					
18.	+								
19.	+		+	+			0		
20.	+		+	+					
21.	+		+	+			+		
22.	0 0 0		+	+	00				
23.	+								
24.	0 0 +								
25.	+				+				
26.	+								
27.	+								
28.	0 0 0 0		+	+	0				
29.	+								
30.	0		+						

+ Positive result.

0 Negative result.

Multiple reports for same procedure represent results of trials on different occasions before treatment.

(+) Positive report following review of same lymph node.

splenic material inoculated into hamsters produced infection in these animals. The average age of the disease when it was diagnosed by spleen puncture was 10 weeks and varied from 2 to 23 weeks. Spleen puncture has not been practiced to any extent in this country and is generally looked upon as a potentially dangerous procedure. In our experience it has proved a simple, safe and very valu-

able diagnostic approach to kala-azar and it seems desirable therefore to describe the technique.

Technique of spleen puncture: (a) This procedure is simple, but it requires the use of great care. If any difficulty is anticipated, lymph node puncture or biopsy or sternal puncture should be chosen for the first trial in diagnosis. Spleen puncture should be performed only in cases in which kala-azar is suspected because of exposure in endemic areas and when clinical data support the diagnostic impression. It should be done only when the edge of the spleen is well below the costal margin. The blood-clotting time and the bleeding time should be determined beforehand. If the clotting time is significantly prolonged, whole blood should be transfused in amounts sufficient to bring it within normal limits.

(b) The procedure should be explained to the patient, with emphasis on the need for him to hold his breath in inspiration at the proper time and on the fact that the puncture takes only a few seconds and is usually painless. It may help rehearse the procedure with the patient.

(c) Only liquids should be allowed for breakfast on the morning the puncture is to be done. Pentobarbital sodium 0.1 Gm ($1\frac{1}{2}$ grains) should be given by mouth 1 hour before puncture. The patient is placed on an abdominal binder (to be used later) and the abdominal skin is cleansed as usual. The site of puncture is selected midway between the edge of the spleen and the costal margin. It should never be immediately below the costal margin or between the ribs. The skin is anesthetized with 1 per cent procaine hydrochloride solution which is injected so as to produce a wheal about 2 cm. in diameter in the skin.

(d) A dry sterile needle of 17 to 19 gauge and $1\frac{3}{4}$ inches in length should be used. It may be introduced with a stylet in place or without stylet and with a sterile air-tight 5 cc. syringe attached. The patient is instructed to breath in and out deeply 10 times and to hold his breath on the tenth inspiration. The operator may count aloud and on the ninth inspiration say, "Now breathe in deeply once more and hold it." The needle is then thrust well into the spleen. It should be held firmly, but not too rigidly. If a stylet is in place, it is withdrawn and a sterile air-tight 5 cc. syringe attached. Suction is produced until a small amount of blood enters the syringe. The plunger is then gently released and the needle is quickly withdrawn. Pressure should be applied gently with the hand over a sterile pad for a few minutes, after which the abdominal binder is closed. The aspirated material should be used for preparing smears and cultures, as described below.

(e) The patient should not have solid food for 2 or 3 hours, and he should remain in bed until the next day. He should be observed closely and the pulse and blood pressure should be taken frequently for 24 hours. Appropriate steps should be taken at once, if any evidence of bleeding is observed.

Smears. Tissue puncture material should be spread as thin as possible, allowed to dry, and, after staining with Giemsa or Wright's stain, should be examined under an oil immersion lens. The examination of stained preparations of such material gives a high percentage of positive results, but long search may be required to find the parasites. In the preparation of smears, large parasitized

mononuclear cells are frequently broken and parasites liberated. As a result, free *Leishman-Donovan* bodies may be found. These must not be mistaken for platelets and hence disregarded; conversely, platelets should not be identified as *Leishman-Donovan* bodies. When doubtful objects are seen, further search should be made for parasites which show typical morphology and leave no doubt as to the identification.

Lymph node biopsy was performed in 7 patients in whom lymphadenopathy was a prominent feature of the disease. In 3 patients the initial biopsy was negative but in 2 of these when the sections were reviewed in the light of additional clinical and laboratory data, *Leishmania* were found. In four additional patients the diagnosis was established from examination of smears or sections of lymph nodes making a total of 6 out of 7 diagnosed as a result of lymph node biopsy. This procedure, a standard simple surgical measure, should be resorted to if lymphadenopathy is present in the course of a clinical entity which may be leishmaniasis. However, if the possibility of this infection is not borne in mind in patients who have lymphadenopathy and have served in endemic areas the parasites may easily be overlooked in a routine examination of sections.

The clinical diagnosis of kala-azar is suggested as a result of awareness of the possibility of this disease in patients who have been in endemic areas and careful consideration of the clinical and laboratory features previously discussed. Prolonged intermittent fever frequently with double daily peaks, enlargement of the spleen, liver, and/or lymph nodes leucopenia, anemia, and elevation of the serum globulin are all highly suggestive of this infection.

Blood smears both thick and thin should be examined and in the latter special attention should be given to studying the edges and end of the smear where the white cells may be aggregated in great numbers for among them may be found mononuclear cells containing parasites. Free parasites may be found in thin films but care must be taken not to confuse them with blood platelets. If lymph nodes are enlarged one may be aspirated or removed and smears and sections made for study. Cultures on NNN medium should also be made with material from the removed node. Sections should be cut relatively thin and examined under the oil immersion lens to avoid overlooking the parasites which suffer considerable shrinkage in fixation. Bone marrow smears and cultures may be diagnostic in 60 to 75% of cases if one or more suitable marrow specimens have been obtained and if care and time are expended in the search for parasites. Finally spleen puncture is to be considered if the other possibilities of diagnosis have been explored without success and due care is given to the details of the technique of this procedure.

Course, Treatment, and Results of Treatment

The average interval from the onset of acute symptoms to definitive diagnosis and the initiation of specific treatment was 10 weeks and varied from 2 to 23 weeks. In 50% of the cases the disease was active and under observation in a military hospital for 3 months or more before the diagnosis was made and in only 5 patients

was the diagnosis established within a month after onset. In 6 patients the disease was continuously active during 4 to 6 months of uninterrupted hospitalized before the correct diagnosis of kala-azar was proved. Delay in diagnosis was not due to difficulty in demonstrating *Leishmania* but rather to lack of awareness of the possibility of kala-azar because once the latter was suspected the diagnosis was usually proved in a short time.

In practically every patient before the diagnosis was established anti-malarial drugs, sulfonamides, penicillin and transfusions were librally used in the hope of combating some infection which could not be demonstrated. In a few patients with severe anemia transfusions were given as a general supportive measure. Several patients developed intercurrent infections (otitis media, pneumonia, and abscess of the buttock following parenteral injection of liver extract) and in them sulfonamides and penicillin were of benefit in overcoming these infections but had no effect on the underlying disease. The outstanding features in the untreated disease were the rapid marked loss of weight, development of moderate to severe anemia, and the progressive enlargement of the spleen and liver. Fortunately, no deaths occurred despite the prolonged course of the disease in many patients before the correct diagnosis was made. This is attributed to excellent nursing care, symptomatic control of intercurrent infections with penicillin and sulfonamides, the liberal use of blood in severe anemia, the relatively good physical condition of the patients at onset, and the absence of associated chronic infections and malnutrition frequently seen in natives with this disease.

Specific treatment with antimony compounds was initiated as soon as the diagnosis was made. The results of treatment are summarized in table 2.

Two patients received 30 and 45 cc. of fuadin (Antimony-III-biscatechol disulfonate of sodium containing 13.5% of antimony) overseas or en route to this country because no other form of antimony was available. No benefit was derived from this treatment. The other patients all received either neostam, neostibosan, or stibanose (pentavalent antimony compounds) in one or more courses of one or several of these drugs. Two failures were retreated with stilbamidine.

Fifteen patients were cured after a single course of one drug; 3 patients after a continued single course of 2 drugs; 9 patients were cured after 2 courses of treatment because of one previous failure; 2 patients were cured after 3 courses of drugs because of two previous treatment failures; and 1 patient required 6 courses of treatment because of 5 prior treatment failures.

Six patients were cured after a single course of neostam (stibamine glucoside) with total doses of 3.4 to 4.05 Gms. (average 3.8 Gm.) when the average age of the disease at the beginning of treatment was 6.3 weeks. Fourteen patients were cured after a single course of neostibosan with total amounts of 2.9 to 5.0 Gm. (average 4.1 Gm.) when the average age of the disease at the beginning of treatment was 18.4 weeks. Three patients were cured after a continued course of one drug followed immediately by a course of another antimonial, as follows: 1 patient, 1.9 Gms. of tartar emetic followed by 2.6 Gms. of neostibosan; 1 patient, 6.4 Gms. of neostam followed by 2.9 Gms. of neostibosan; and 1 patient,

TABLE 2

Results of treatment in 30 proven cases of kala-azar

CASE	T.	FUADIN	TARTAR EMETIC	NEOSTAM	NEOSTIBOSAN	STIBANOSE	STILBAMIDINE
		cc.	*Gm.*	*Gm.*	*Gm.*	*cc.*	*Gm.*
1.	I				3.5[r] 5.0*		
2.	I				2.9*		
3.	I			3.6[r] 4.25[r]	5.0*		
4.	I					200*	
5.	I			4.05*			
6.	M			3.5[r]	3.9*		
7.	M	30[f]		2.9[r]	3.9*		
8.	M			3.5*			
9.	M				3.6*		
10.	I				5.1*		
11.	M				3.6*		
12.	M			3.9*			
13.	M				4.7*		
14.	I			6.4†	2.9†		
15.	M			3.9*			
16.	M				3.9*		
17.	I			4.7[r]	2.4[r] 5.0*		
18.	M			4.0[r]	5.0*		
19.	I	43[f]		0.8[f]	2.7[r] 5.0[r] 10.0[r]	240[r]	4.0*
20.	I			4.6[r]	5.0*		
21.	M			4.5[r]		200*	
22.	M				5.0*		
23.	M					200[r]	4.0*
24.	I			3.8*			
25.	M		1.9†		2.6†		
26.	I			3.8*			
27.	I			2.6†	2.6†		
28.	M			2.5[r]	5.0*		
29.	I				3.4*		
30.	I				3.4[r] 5.0*		

[f] No effect.
[r] Clinical improvement followed by relapse.
* Drug and amount which produced cure.
† Continuous course of two drugs which produced cure.

Summary of relative efficiency of drugs

TREATMENT	PATIENTS	NO. TREATMENTS	% TREATMENT CURES	% PATIENTS CURED
Fuadin	2	2	0	0
Neostam	14	15	40	42
Stibanose	4	4	50	50
Neostibosan	18	23	74	95
Stilbamidine	2	2	100	100

2.6 Gms. of neostam followed by 2.6 Gms. of neostibosan. One patient was cured with a single course of 200 cc. of stibanose (sodium antimony gluconate, [redacted]

20 mg. antimony per cc.) and one patient was likewise cured with the same amount of this drug after previous failure with 4.5 Gms. of neostam. Neostam given alone failed in 9 patients who received from 2.5 to 4.7 Gms. (average 4.0 Gms.) when the disease was of an average duration of 11.1 weeks at the beginning of treatment. All treatment failures (11 patients) were cured with neostibosan, 3.9–5.0 Gms. (average total dose 4.8 Gms.) with two exceptions (Cases 19 and 23). Thus, of 14 patients who received neostam there were 8 or 57% failures. The average total amount of neostam for the cures was 3.8 Gms.; and for the failures, 3.9 Gms. In contrast to failure from neostam given alone, of 10 patients who received neostibosan as initial treatment there were only 2 failures (average total dose 2.9 Gms.). Of a total of 18 patients who received neostibosan initially or after previous treatment failure (average total dose 4.5 Gms.) there was only one failure or a failure rate of 6% compared to 57% failures for neostam.

The average interval between the beginning of treatment and freedom from fever was 12 and 22 days, respectively, for neostibosan and neostam. The immediate effect on the rate of control of fever in this series is not related to subsequent success or failure of treatment. The disappearance of fever seemed to be more prompt in patients who had had no prior treatment. Neostibosan produced a more prompt control of fever than neostam in cases of both Indian and Mediterranean origin, however, whether the latter were of short or long duration and regardless of prior treatment failures.

The average duration of fever in 4 patients who received 20 cc. of stibanose daily (total dose 200–240 cc.) was 5.2 days. No toxic experiences were encountered with this drug in these 4 patients nor in 4 additional patients who received 200 cc. experimentally for schistosomiasis japonica nor in 1 patient with filariasis bancrofti who received 400 cc. during 20 days. One patient who was not cured with 5.0 Gms. of neostibosan was likewise not cured with 240 cc. of stibanose. One additional patient not previously treated was not cured with 200 cc. stibanose. This drug appears to control fever promptly and is apparently not toxic. In our limited experience it has been found inferior to neostibosan in respect to ultimate cure, however.

Toxic symptoms were encountered in the majority of the patients who received neostam. These consisted principally of severe nausea and vomiting and in one patient shock and convulsions followed a single dose of 0.3 Gms. No symptoms of toxicity were observed in 18 patients who received neostibosan. One patient received 0.5 Gms. daily for 20 consecutive days without symptoms or signs of toxicity. However, one patient subsequent to a course of 3.9 Gms. of neostibosan developed a kidney lesion characterized by fixed urinary specific gravity, diminished output of P.S.P. and constantly elevated blood urea nitrogen without hypertension or proteinuria. These changes persisted during a period of observation of 6 months after treatment. This is a very uncommon manifestation of antimony toxicity and may be encountered during or after treatment with both trivalent and pentavalent compounds.

Neostibosan appeared to be equally effective in this series in curing infections of Mediterranean or Indian origin and infections of short or long duration pro-

vided the total dose was at least 4.0 Gms. although several patients were cured with smaller amounts of this drug. Neostam failed as often in Indian as in Mediterranean infections without relation to age of disease. Dosage was not the crucial factor in failure with neostam. Six failures occurred with more than 4.0 Gms. of neostam while only one failure occurred with more than 4.0 Gms. of neostibosan.

It is evident from consideration of these data that on the basis of total dosage, resultant cures, clinical effectiveness, and toxicity, neostibosan was superior to neostam in treating kala-azar of short or long duration, whether of Indian or Mediterranean origin. Failures were principally the result of the use of neostam overseas or in a few hospitals in this country or to inadequate dosage with neostibosan.

In one patient antimony resistance may be responsible for repeated failures. This patient received small amounts of fuadin, neostam, and neostibosan overseas. At Moore General Hospital he received 5.0 Gms. of neostibosan, 240 cc. stibanose and 10.0 Gms. of neostibosan with only temporary benefit after each course. Following an interval of a month or less after each of these courses of treatment fever returned and splenic smears remained repeatedly positive. Cure was ultimately accomplished with stilbamidine (4.0 Gms.). The treatment and response to various amounts of drugs in this patient is shown in fig. 2.

The specific treatment of kala-azar with neostibosan is indeed very simple. It has been our practice to administer a total dose of 5.0 Gms. in 17 days or less. Neostibosan (diethylamine p-aminophenyl stibinate), a light brownish powder containing 42% antimony is available in ampoules each containing 0.3 gms. The contents of an ampoule are dissolved in sterile saline or distilled water to make a 5% solution (6 cc.). The first dose usually is 0.2 Gms. (4 cc.) and is given intravenously. Subsequent doses are 0.3 Gms. (6 cc.) and are given daily until a total of 5.0 Gms. have been given. In several patients we have given this total dose in 10 days (0.5 Gms. daily) with excellent results and without symptoms or signs of any kind of toxicity. A liberal fluid intake is encouraged during treatment and a liberal diet compatible with the patient's appetite is prescribed. We did not give adjuvant therapy in the form of iron, vitamins, or liver extract. Hematologic recovery following adequate neostibosan therapy alone was complete. If intercurrent infections or complications during specific therapy should occur, the latter should not be interrupted or discontinued unless there is evidence that the difficulty is directly related to antimony. This was not observed in any of our cases. Penicillin and/or sulfonamides may be given to control bacterial infections during treatment with neostibosan. Moderate to severe anemia associated with kala-azar responds to adequate neostibosan therapy and we did not in any case find it necessary to resort to transfusion as a symptomatic measure after starting treatment.

The response to treatment is frequently dramatic. Fever which may have been a feature of the disease for months may disappear in as short an interval as 3 days after the first dose of drug. The average interval to freedom from fever after the beginning of neostibosan therapy in this series was 12 days. Most

patients have a normal temperature when about half of the total amount of drug has been given although a few patients may still have a low grade fever for 7

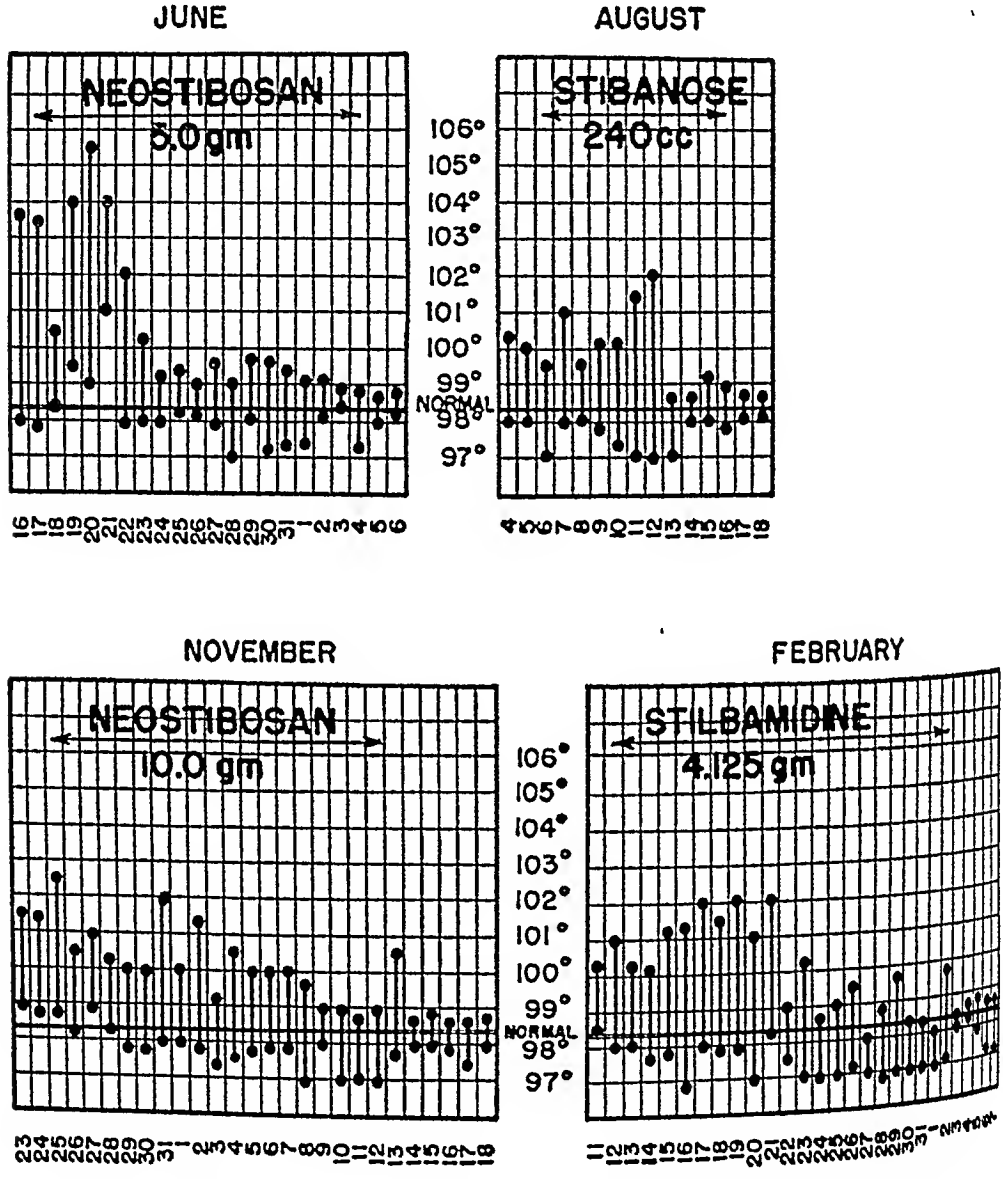
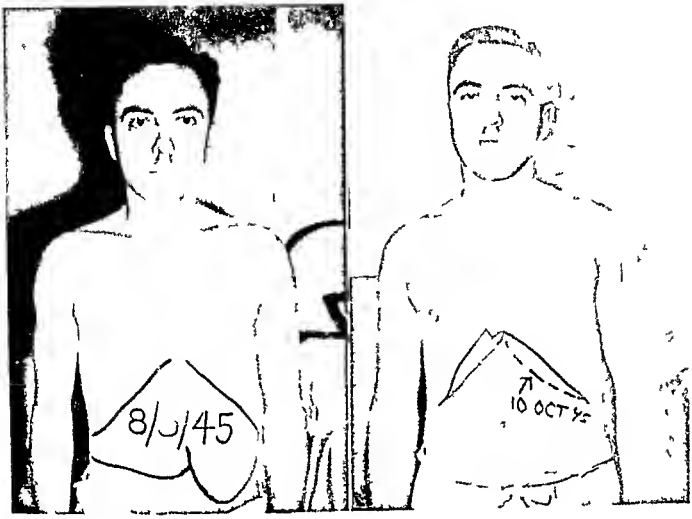


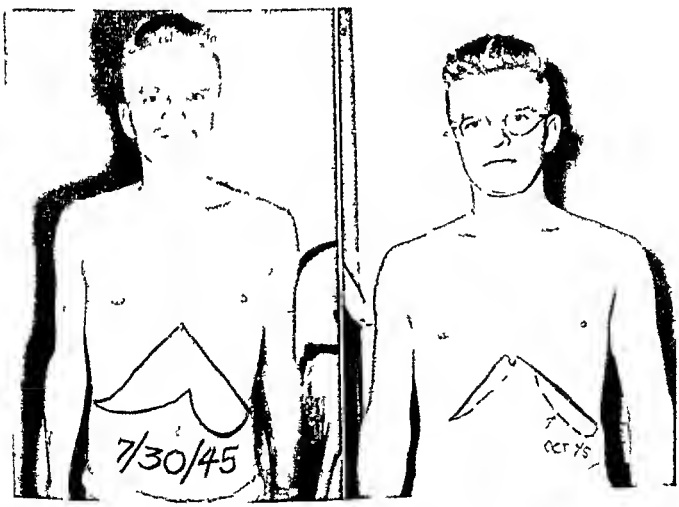
FIG. 2. RESPONSE OF TEMPERATURE TO FOUR COURSES OF TREATMENT IN THE SAME PATIENT (CASE 19)

Note that fever subsided promptly after each course of treatment but relapse occurred after each course but the last. This patient had received before the first course shown in the figure small noncurative amounts of fuadin, neostibosan, and neostam and as a result may have developed an antimony resistant strain of *Leishmania*. Relapse occurred even after 10.0 Gms. of neostibosan. Stilbamidine is recommended only after relapse following adequate amounts of antimony. The necessity of prolonged observation after treatment is apparent from this case.

to 10 days after completion of treatment. In some patients the maximum daily temperature becomes progressively lower with each day of treatment and gradually the temperature becomes normal. In other patients chills and high fever continue daily for the first 5 to 8 days of treatment and then suddenly the



CASE 3



CASE 4

FIG 3 ENLARGEMENT OF LIVER AND SPLEEN IN PATIENTS WITH KALA AZAR AND RESPONSE TO TREATMENT

Note marked diminution in size of liver and spleen within a month after completion of treatment Note also improved nutritional state

temperature becomes normal and remains so during the remainder of treatment and thereafter. Striking responses to treatment are shown in figs. 1a, 1b and 2.

Symptomatic improvement is frequently noted by the patient within a few days after treatment is begun. With subsidence of fever and disappearance of chills and drenching sweats the appetite becomes progressively better and in some patients the amount of food consumed is amazing. One patient gained 30 pounds in weight during the first 5 weeks from the beginning of treatment and in most patients normal weight has been restored within 3 to 8 weeks after treatment has been completed. The spleen frequently shrinks very rapidly during treatment. In one patient who had been sick for 6 months before treatment was

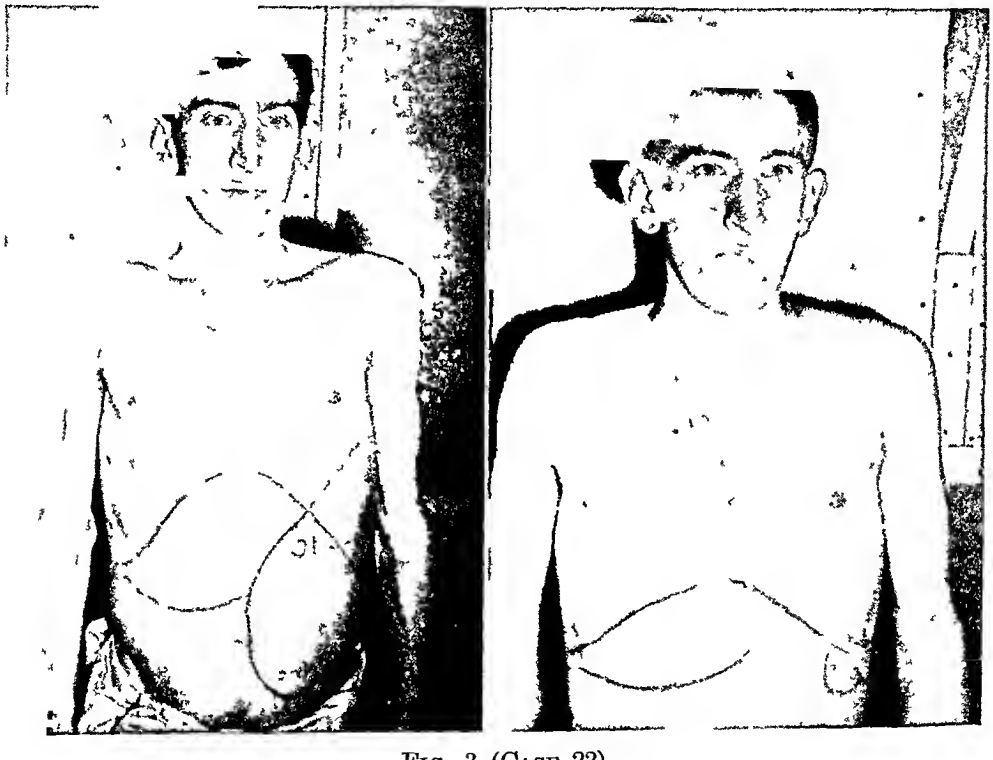


FIG. 3 (CASE 22)

begun and in whom the edge of the spleen was in the pelvis, the spleen at the end of a month after the beginning of treatment was barely palpable. In practically all patients the spleen was no longer palpable within two months after completion of treatment. Typical changes in the size of the spleen and liver after treatment are shown in fig. 3. Anemia corrects itself after successful treatment and frequently a striking reticulocyte response is observed during therapy. The white blood count rises gradually and is usually normal within a month after completion of treatment. The alterations in the serum proteins which are so striking in this disease change but slowly during or after treatment and it may be 6 months before a normal balance has occurred in the relationship of the various serum protein constituents. The details of the hematologic and

biochemical changes observed in this series of kala-azar and the response during and after treatment are fully discussed in the laboratory section of this paper.

Complications related to treatment or occurring during the course of the disease in our patients were very infrequent. One patient developed pneumonia before the diagnosis of kala-azar was established, and in 2 other patients pneumonia complicated the disease during antimony therapy or shortly after its completion. In these cases penicillin effectively controlled the intercurrent pulmonary infection. One patient who had previously had acute otitis media developed an acute exacerbation during treatment with neostibosan. Penicillin was given for several days without interrupting the regular neostibosan schedule and this complication was promptly controlled. One patient, while under observation overseas, developed a gluteal abscess following the administration of liver extract parenterally. Incision and drainage and penicillin controlled this infection. It is of practical interest that intercurrent bacterial infections in two of our patients was associated with leucocytosis (13 to 20,000) and that when the infection was controlled the white count returned to its previously low level. Fortunately no mouth complications (ulcerative stomatitis) occurred in this series. This may be due to the relatively healthy state of the mouth in our patients compared to natives in whom this complication does occur. Acute agranulocytosis related to the disease or to antimony did not occur. This rare complication has been described (10) in relation to the disease or its treatment and may be recognized clinically and by frequent observations of the white blood count and differential. If it occurs during antimony treatment the latter is suspended until the complication has been overcome (blood transfusions, penicillin, crude liver extract) and antimony treatment again instituted when the general condition of the patient and white blood count and differential are such as to warrant further specific therapy.

Treatment failures which we have observed here or which occurred overseas may be classified in two categories. In one group are patients who show only minimal or no response during treatment or for a month after its completion. Such failures were observed with fuadin and neostam and were manifested by little or no effect on fever during or after treatment. The liver and spleen remained enlarged, anemia did not improve, and the white count remained at a low level. In the second group of failures there is a satisfactory response to treatment, i.e. fever is controlled, anemia improved, the white count rises, the spleen begins to shrink, and the patient is clinically better. But, after an interval of several weeks or months following treatment, fever recurs and there is clinical and laboratory evidence that the disease is active again. The average interval to relapse following neostibosan treatment was 5.8 weeks (range 4 to 13 weeks) and 5.2 weeks (range 1 to 16 weeks) after neostam. It is therefore advisable to have patients under continued observation for at least 4 to 6 months after completion of treatment. In this series all patients were observed for more than 16 weeks after completion of therapy, the average being 6 months.

While relapses, in most cases, are readily apparent within 2 months of treatment, there are instances of late relapses. Two of our cases, with good initial response

to treatment, were suspected to have relapsed only after 4 months of continued observation after treatment. One (Case 30) was clinically well at this time, but was not discharged because leukopenia persisted. In the next two weeks the weight fell 10 pounds. In the other (Case 23), the patient was improved in all respects at 4 months, but weight and strength were still subnormal. Sternal puncture done 3 weeks later revealed viable *Leishmania*. These patients were re-treated, although it is conceivable that they might have gone on to cure without further treatment.

The most common symptom which is indicative of relapse is the return of fever. The other clinical and laboratory features associated with active kala-azar are likewise again observed. In this series spleen punctures were performed in all relapses and were found positive in every case. However, a positive spleen puncture one to two months after treatment is by itself not evidence of treatment failure or relapse since in several instances we obtained viable *Leishmania* from the spleen 4 to 8 weeks after treatment and cure followed without any further treatment. Nevertheless, spleen puncture is important in excluding suspected relapse especially if no *Leishmania* are found on smear or culture. Such negative findings make it necessary to look for causes other than active kala-azar as an explanation for the fever or other clinical findings before additional antimony or other therapy is contemplated. In this series, treatment failures or relapse were the result of inadequate amounts of neostibosan in several patients or followed neostam in more than 50% of the patients who received the latter drug irrespective of total dose. In one patient antimony refractoriness was the probable explanation for repeated relapse after each of several intensive courses of neostibosan and stibanose. This patient had previously received small amounts of fuadin, neostam, and neostibosan with only temporary improvement after the latter two courses. Ultimately cure followed the administration of 4.0 Gms. of stilbamidine (4:4′ diamidinostilbene). This drug, a non-metallic organic compound, has been found to be effective in treating antimony resistant strains of *Leishmania* (Sudan) as well as the more readily susceptible strains (India, China, Mediterranean). Stilbamidine is a potentially dangerous drug which may prouce shock, hemolysis, hepatic necrosis, and severe neuritis and should therefore be used with caution and only after failure with several intensive courses of neostibosan. There is some indication that the more serious toxic reactions do not occur if solutions are prepared daily before use. This was done in our cases.

In treating a relapse consideration must be given to the number of previous relapses, the origin of the infection, and the drug and total doses previously used. If relapse has followed neostam or amounts of neostibosan of less than 5.0 Gms. re-treatment should consist of the administration of at least 5.0 Gms. of neostibosan as outlined in this report. Relapse after 5.0 Gms. of neostibosan can be re-treated with 10.0 Gms. of the same drug, (0.5 Gms. daily for 20 days). Relapse after 10 Gms. should be re-treated with stilbamidine.* Our experience

*Pentamidine is now recommended instead because it is less toxic and apparently as effective as stilbamidine.

with this drug is limited to 2 patients. Each dose is given intravenously in at least 200 cc. of fluid beginning with 25 milligrams and increasing the dose daily by this amount until a daily dose of 300 milligrams is reached. More concentrated solutions produce local phlebitis. Transitory flushing and anorexia occur commonly but have no serious import. The total dose in our patients was 4.0 Gms. although the usual curative dose is said to be between 1 and 2 Gms. In

TABLE 3

Serum proteins before any specific therapy

CASE NO.	ALB.	GLOB.	TIME FROM ONSET OF SYMPTOMS
	Gm. %	*Gm. %*	*days*
10	4.1	2.1	9
10	4.2	2.2	27
10	3.8	2.0	37
16	2.8	5.2	152
16	3.1	6.2	168
24	3.1	4.6	61
28	3.9	5.1	40
30	3.4	4.5	54
22	3.5	3.5	70
18	5.7	4.0	59
27	3.2	4.1	18
11	3.2	3.6	53
23	3.0	5.8	123
19	3.7	4.1	134
4	4.1	3.1	97
9	3.5	3.9	83
9	2.7	3.9	115
9	2.9	4.2	117
20	3.8	3.7	77
12	4.8	8.0	81
1	3.2	3.8	56
13	4.9	3.1	39
13	4.5	3.5	186
13	4.0	5.9	223
14	3.1	2.9	61
6	4.8	2.7	62
6	3.4	6.8	120

the event of repeated relapse following intensive therapy with neostibosan and other pentavalent compounds a trial with tartar emetic (potassium or sodium antimony tartrate) may be attempted. This might also be used when other drugs are not available. A satisfactory dose schedule is as follows: Day 1, 10 cc. of freshly prepared 0.5% solution; Day 3, 20 cc.; Day 5, 30 cc.; and the latter dose continued every other day until a total of 360 cc. (1.8 Gms.) have been given. Toxic manifestations consist of a dry hacking cough immediately after an injection, severe joint and muscle aching which begin 6 to 12 hours after the injection and disappear about 12 hours later, nausea, and electrocardiographic

changes (principally inversion of T waves). Severe cough can be minimized or avoided by giving the 30 cc. doses in 2 injections of 15 cc. each with an interval of 1 hour between the injections. The rate of injection should not be more rapid than 1 cc. in 15 seconds.

Failure following intensive pentavalent and trivalent antimony and stilbamidine treatment is rare. Careful clinical and laboratory studies are necessary to determine whether some other condition, not kala-azar, is responsible for the continued illness of the patient. Recently a patient with kala-azar unsuccessfully treated with several intensive courses of pentavalent antimony compounds and stilbamidine was submitted to splenectomy. A dramatic clinical and hematologic response followed (11). Splenectomy must, therefore, be considered as a last resort if all other attempts at treatment have failed.

CLINICAL PHYSIOLOGY

Serum Proteins Before Treatment

Observations before institution of any specific therapy were available in 18 of the cases. They were made within one month of the onset of symptoms in 2 cases, within 2 months in 8 more, and up to 5 months in the remainder. In 5 cases, more than one pretreatment observation was made. The data are presented in table 3.

Serum albumin is seen to be below 4.0 Gms. per cent with few exceptions. It is 3.5 or less in 11 of the 18 cases. It is less than 3.0 in only 2 cases, the lowest value being 2.7 per cent.

Serum globulin exceeds 2.5 per cent in all but one case. Of the two cases observed within one month of the onset of symptoms, one is the exception noted above, with globulin of 2.0 per cent. The other had a globulin of 4.1 per cent; this patient had a concurrent hepatitis, probably unrelated to the leishmaniasis. Of 9 observations in the second month after the onset of symptoms, globulin was 4 or greater in four; 3.8, 3.6, 3.1, 2.9, and 2.7 in the remainder. Globulin exceeded 3.0 in each of 10 observations in the 3rd, 4th, and 5th months, and it exceeded 5.0 in half of these.

In summary, fall in albumin and rise in globulin were regularly manifested within 2 months of the onset of symptoms. Hyperglobulinemia became marked, but hypoalbuminemia never became severe in this series, though more extreme values have been reported (12) (15).

Response of Serum Proteins to Treatment

Data before institution of curative therapy and at intervals thereafter are presented in table 4. Hypoalbuminemia and hyperglobulinemia are evident before treatment. After institution of therapy serum albumin rises to exceed 4.0 per cent in 1 to 2 months, with few exceptions. Maximal values are usually attained 3 months after the start of treatment. Serum globulin returns to normal limits more slowly, remaining above the normal limits in the majority of cases

even after 5 months. The course of the serum proteins in 3 cases in relation to onset of symptoms and to therapy is presented graphically in fig. 4. Note the slow descent of globulin into the normal range, the reversion of the formol gel test to normal shortly after treatment, and the prolonged persistence of positive cephalin flocculations.

TABLE 4

Serum proteins in relation to start of successful therapy

CASE NO.	BEFORE THERAPY		1 MONTH AFTER		2 MONTHS AFTER		3 MONTHS AFTER		4 MONTHS AFTER		5 MONTHS AFTER		6 MONTHS AFTER		7 MONTHS AFTER		8 MONTHS AFTER		9 MONTHS AFTER	
	Alb.	Glob	Alb.	Glob	Alb.	Glob.	Alb.	Glob	Alb.	Glob.	Alb.	Glob.	Alb.	Glob.	Alb.	Glob.	Alb.	Glob.	Alb.	Glob
3	4.7	3.0	4.8	3.5	5.2	2.0			5.3	2.3										
10	3.8	2.0	5.4	2.2	4.4	1.9														
15							4.1	5.1											5.5	2.5
16	3.1	5.2					3.4	5.3	4.5	4.1	4.2	3.6			5.2	2.6				
17	4.3	3.1	4.8	2.0			5.4	1.4			5.2	2.0								
24	3.1	4.0							4.5	3.8			4.8	3.3			4.0	2.4		
28	3.0	5.8	3.7	6.0	4.1	4.5			4.8	2.7										
26											5.4	1.5								
30	3.4	4.5			4.6	4.0			4.8	3.6										
22	3.0	5.5	4.4	3.7	4.8	2.6	4.7	2.0	4.8	2.4					5.2	2.1				
21	3.2	5.8	3.5	4.7	3.7	5.1			3.9	5.3	4.2	5.0	4.1	4.4						
18	3.0	5.4					5.1	2.8			4.0	3.0								
27	3.2	4.1					5.2	2.0			4.8	1.9								
11	3.0	4.0			4.0	5.5	4.1	3.4			4.2	3.7								
23	3.0	0.2	3.1	5.7	3.3	4.7			2.7	6.2*										
10	3.7	5.9	3.5	0.4	4.4	3.8	4.8	3.3	4.4	3.1	5.1	2.2								
5			4.3	4.2			3.6	3.1	3.5	2.9			3.0	3.2	4.8	2.8			5.1	2.0
4	4.1	3.1	4.7	3.4	4.8	3.3			5.2	3.2										
0	2.9	4.2	4.4	3.2			4.2	3.2			4.2	2.0								
25			4.0	4.0			4.0	2.0			4.7	2.5			5.0	2.1				
20	3.9	4.5	4.0	3.0			5.5	2.3	4.9	2.9	5.0	2.8								
12	4.8	8.9	2.3	10.1	3.4	7.4			4.4	5.2	4.2	4.4	5.1	3.8						
1	4.0	4.4	3.7	4.0	4.0	2.8	4.5	2.7			5.2	2.3	4.5	2.5						
2					5.4	1.3	5.4	1.3	5.3	1.8			5.0	1.5						
13	4.0	5.0	3.5	5.1	3.5	5.1	4.8	3.0	4.9	3.3	4.7	3.1	5.0	2.6						
7	3.8	4.6	5.2	3.3	4.3	2.8			5.5	1.7										
6	3.1	6.5	3.4	5.8	5.0	4.3	4.3	4.6			5.2	3.3			5.2	2.1				
14							5.0	3.3			4.5	3.1								
8			4.2	7.1	3.7	0.7			4.4	4.5	4.7	3.7	4.5	3.5						
29					4.5	4.5			5.0	3.3										

* This patient convalescing from acute lymphogranuloma inguinale.

The fall in serum albumin during the first few days of treatment in Case 3 is not accidental. Of 8 cases in which determinations were made during the first week of treatment, fall in albumin of 0.4 Gm. per cent or more was noted in 6 cases at some time between the 2nd and 7th days of treatment. Although hemoglobin and red blood count usually fall as well during this period, the phenomenon is probably not due to blood dilution since globulin usually increases, and the white blood cells and platelets may decrease disproportionately. It seems probable that these phenomena are all related to an initial stimulation of the *Leishmania*.

Phenomena due to Hyperglobulinemia

Several phenomena dependent largely on hyperglobulinemia have been used in the diagnosis of leishmaniasis. These are flocculation of proetin from blood or

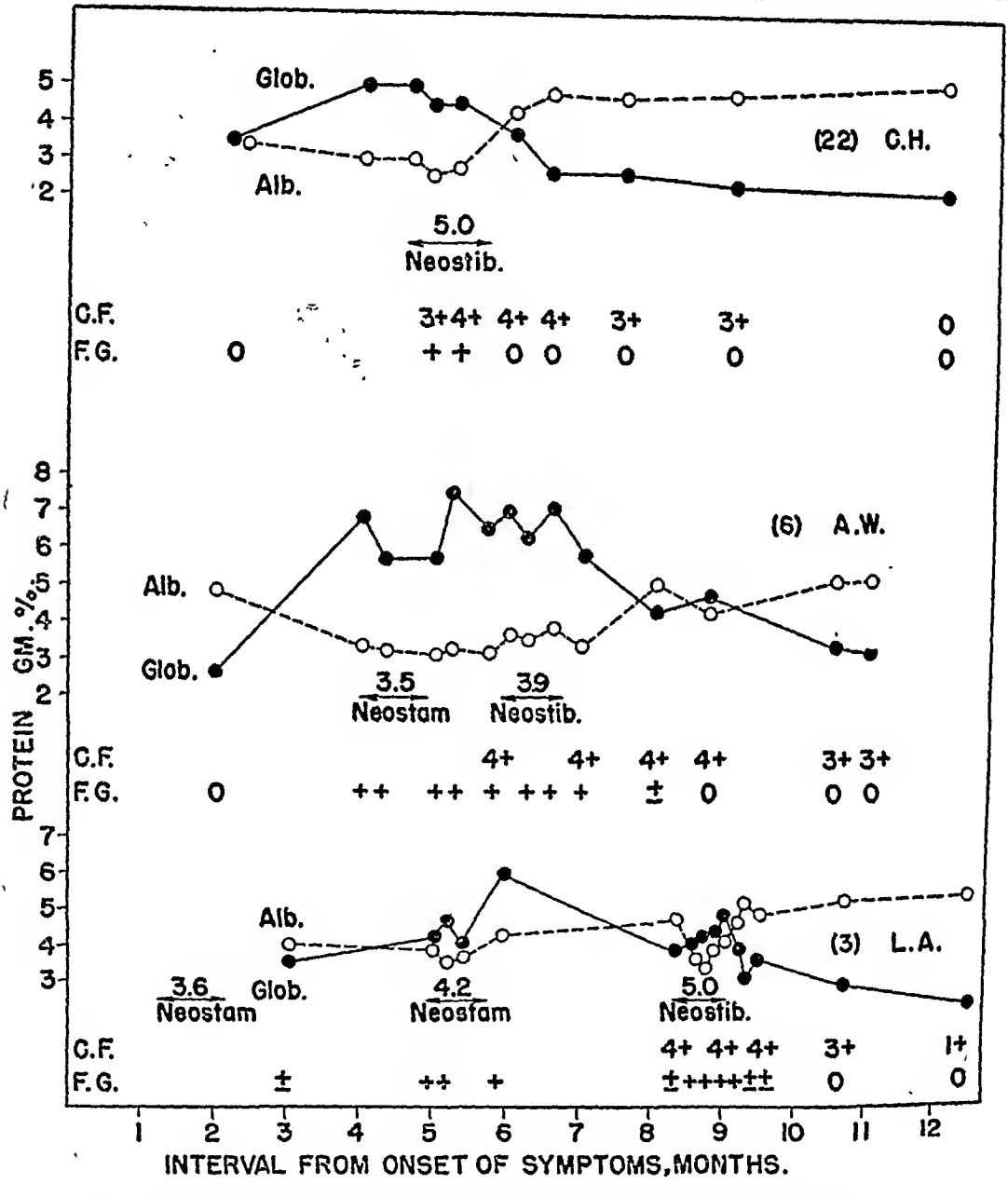


FIG. 4. COURSE OF SERUM PROTEINS, FORMOL GEL TEST AND CEPHALIN FLOCCULATION BEFORE, DURING, AND AFTER SPECIFIC ANTIMONY TREATMENT IN INDIVIDUAL CASES

Note slow fall of globulin, persistence of positive cephalin flocculation test, and more prompt reversion of serum albumin and formol gel to normal.

serum by dilution with water, flocculation from serum by solutions of pentavalent antimony compounds, and *opalescent* gel formation when 2 drops of 40 per cent formalin are mixed with 1 cc. of serum (Napier's formol-gel test). Two or more of these tests were run on the same serum in 14 instances in our series,

with agreement between the various tests except in 2 instances. In one of these the dilution flocculation was negative while the formol-gel was positive; in the other, the antimony test was negative while both the dilution flocculation and the formol gel test were positive. The formol gel test was done 31 times in untreated cases in this series. It was positive 8 times, doubtful twice and negative 7 times in the first 3 months after onset of symptoms, positive twelve times and negative only twice after 3 months.

Serum globulin values and the formol gel test in kala azar before and after treatment

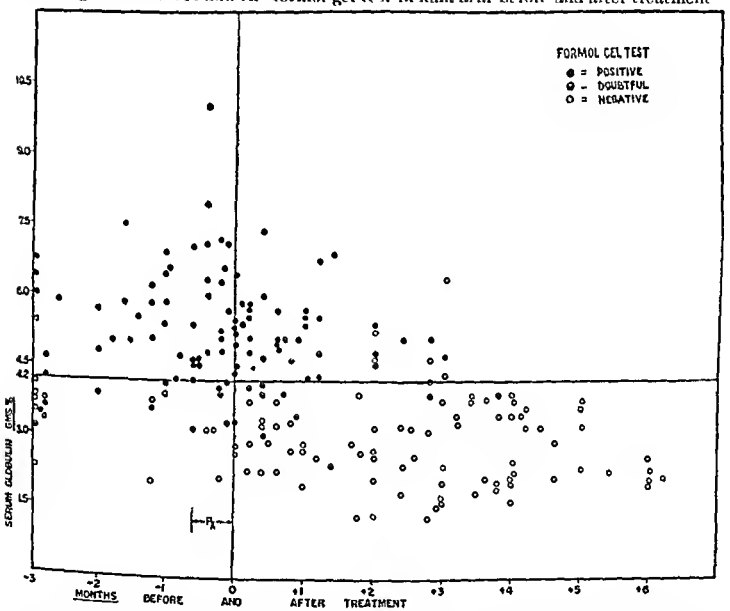


FIG. 5. CORRELATION OF SERUM GLOBULIN AND RESULT OF FORMOL GEL TEST
Note that when the serum globulin is 4.2 Gms % or above, the formol gel test is positive in most instances. Note also that the serum globulin may be elevated for as long as 6 months after completion of successful treatment although the formol gel test becomes negative within a month after treatment. See text for discussion of effect of albumin on formol gel test during and after treatment.

The formol gel test has been shown to depend primarily upon hyperglobulinemia (21). Positive test may be obtained in other diseases characterized by hyperglobulinemia. In our cases, the test was usually positive when serum globulin was 4.2 per cent or greater, fig. 5. In some instances, however, the formol-gel was negative (firm *clear* gel) while globulin exceeded 4.2. This was true usually in the month or two after completion of successful treatment, when serum albumin had increased considerably before serum globulin had fallen markedly. Occasionally a doubtful positive becomes definitely positive during treatment (7). This was observed twice in our series (Case 3 and 19) on the 3rd

and 4th days of treatment respectively at which time serum albumin had decreased 0.9 and 0.6 Gms. per cent respectively from pretreatment levels. It seemed probable from these observations that opalescence of gel is inhibited strongly by albumin.

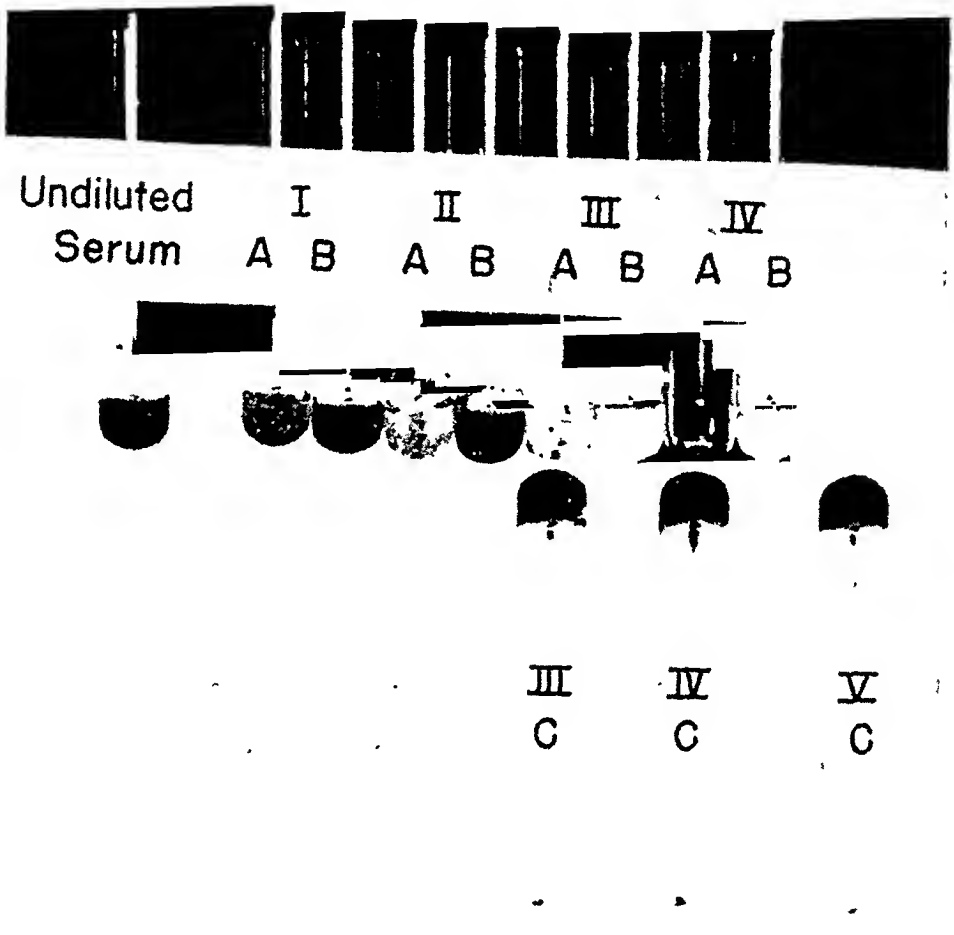


FIG. 6. THE EFFECT OF ALBUMIN ON THE FORMOL-GEL REACTION
Serum from case 23 was diluted I. 20%, II. 30%, III. 40%, IV. 50%, and V. 60% with A. 17% solution of normal human albumin in physiological saline solution, B. Normal serum, and C. Physiological saline solution. One-half cc. portions of the above were mixed with 1 drop of commerical formalin in 8 mm. tubes. Photographs were made with the samples lying on a black background after 24 hours.
Note marked diminution of opalescence in I A; its almost complete disappearance in II A; and loss of gelation as well in IV A. This is in striking contrast to the gelation and intense opalescence after even greater dilution with physiological saline in V C. The dilution with normal serum gives intermediate results.

This was confirmed by *in vitro* experiments as follows: (1) The addition to a strongly positive serum of increasing amounts of a concentrated solution of normal human albumin prevented opalescence first and gelation later. Equivalent dilution of the same serum with physiological saline solution only intensified the opalescence of the gel (see fig. 6). This phenomenon was demonstrated in

each of 4 different sera. (2) A strongly positive serum concentrated by ultrafiltration so that both albumin and globulin were doubled yielded a tough gel without the slightest opalescence (negative test). Dilution of the concentrate with physiological saline solution (or with ultra-filtrate from the same serum) again yielded strongly *opalescent* formol gels. This was demonstrated in each of 4 different sera. (3) Moderate dilution of a positive serum with physiological saline solution only increased the opalescence obtained in the formol test. In one instance, a serum which gave a doubtful positive test (a gel opalescent only against a dark background) with albumin 4.0 and globulin 5.2 per cent was diluted with physiological saline to yield a definitely positive test when albumin was 2.8 and globulin 3.6 per cent. It seems clear, therefore, that the opalescence of the formol gel reaction in the serum of patients with kala-azar is dependent not only upon the hyperglobulinemia but also upon hypoalbuminemia. Opalescent gels may be obtained with normal euglobulin in physiological saline solution. Gel formation is common in sera with elevated globulin content in conditions other than kala-azar, but opalescence of gel is rarely as marked, despite equal reduction in albumin concentration. This suggests that the globulin in kala-azar yields stronger opalescence than that of other conditions in which hyperglobulinemia occurs.

The cephalin flocculation and thymol turbidity tests are dependent upon hyperglobulinemia primarily and, at least in the former, upon hypoalbuminemia secondarily. The cephalin flocculation is regularly 4+ in active cases, the reaction being so strong that flocculation often begins within 5 minutes of the addition of the cephalin suspension. The thymol turbidity is regularly strongly positive, usually being 3 or more times the accepted upper limit of normal. Both tests remain positive for months after successful treatment, even after the globulin concentration has fallen into the normal range. The slow fall of globulin concentration to the normal range suggests that some of the globulin peculiar to leishmaniasis is still present in the serum at this time. It is presumably this globulin, and not liver disease, which is responsible for the positive tests at this time. This will be discussed further in connection with liver function.

Nature of the Hyperglobulinemia

The increase of globulin in these cases, as in previously reported ones (12) (15) is chiefly in the euglobulin fraction.

Electrophoretic studies were made in 2 of our cases through the kindness of Dr. Dan Moore of the Dept. of Anatomy, Columbia University. The curves (fig. 7) indicate an increase in gamma globulin to exceed albumin, without abnormal concentration of alpha or beta globulin.

A cold precipitable protein has been described in the serum in leishmaniasis (13) which redissolves readily on return to room temperature. This phenomenon has been observed in approximately one-third of our active cases. In one, in which it was unusually marked, 1.9 Gms. of protein per hundred cubic centimeters came out of solution at 5° C.

The globulin in leishmaniasis sera binds subnormal amounts of calcium. Total serum calcium is normal or slightly subnormal in the presence of marked

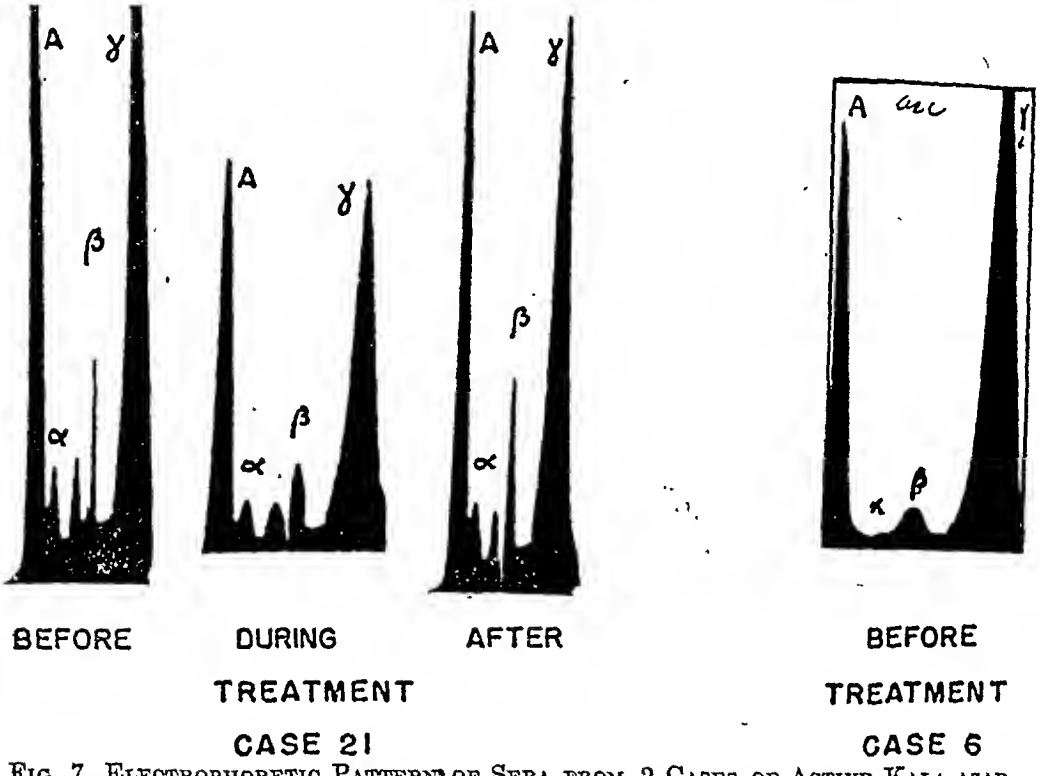


FIG. 7. ELECTROPHORETIC PATTERN OF SERA FROM 2 CASES OF ACTIVE KALA-AZAR
In both instances gamma globulin makes up more than half of the total protein and albumin, little over one-fourth the total. There is no significant change during or immediately after completion of treatment in case 21 (200 cc. stibanose during 10 days). These studies were made by Mrs. M. Costello and Dr. Dan Moore in the Dept. of Anatomy, College of Physicians and Surgeons, Columbia University.
A-albumin; γ-gamma globulin; β-beta globulin; α-alpha globulin (1 and 2).

TABLE 5

Calcium in serum and in ultrafiltrate of serum in leishmaniasis

CASE NO.	SERUM ALB.	SERUM GLOB.	SERUM CALCIUM	ULTRAFILTRATE CALCIUM
	%	%	mg. %	mg. %
15	3.3	7.0	9.5	
11			9.2	
9	2.5	6.1	9.0	
12	4.8	8.9	10.0	
19	3.6	6.4	9.7	5.4
21	3.9	5.3	10.4	6.2
23	3.1	6.1	9.0	5.7
28	2.5	6.4	10.3	6.3

hyperproteinemia, while untrafiltrable calcium is within normal limits (table 5). This has previously been shown to be true in the hyperglobulinemia of certain other diseases, in which subnormal base-winding of the proteins has also been demonstrated (14).

The globulin peculiar to leishmaniasis is, in summary, a sparingly soluble gamma globulin which binds subnormal amounts of calcium (and presumably of total base as well). It seems probable that it arises in an immune reaction, or, conceivably, from continuous destruction of parasitized reticulo-endothelial cells.

Incidence and Speed of Development of Leukopenia

Records of counts done early in the disease are available in most instances. Of 11 cases first observed within 10 days of the onset of symptoms, none had leukocytosis; 3 had counts less than 4000; and 4 more, with total counts between 4 and 6000, had mild granulopenia (less than 3000 polymorphonuclear cells per cu. mm.). Of 9 cases first observed between 11 and 30 days after onset of symptoms, none had leukocytosis; 5 had counts less than 4000; and 2 more, with total counts of 4200 and 5900, had mild granulopenia (1800 and 2100 polymorphonuclear cells per cu. m., respectively). Of 8 cases first seen later than 1 month from the onset of symptoms, the count was less than 4000 in all but one instance (Case 4), in which case it was 4600. The latter observation though 42 days from the onset of symptoms, was only 10 days from exacerbation of fever following a spontaneous remission. Two weeks later the count fell below 3000. At the time of first observation, then, 15 of the 28 cases had counts less than 4000, and 6 more, with counts between 4 and 6000, had polymorphonuclear cell counts of less than 3000 per cu. mm. Of the six men whose initial observation exceeded 4000 but who had mild granulopenia, 5 had total counts less than 4000 within a few days of initial observation. Two others with initial counts of 5000 and 7700 fell well below 4000 during the first month of disease. Thus, only 2 of the 20 cases observed in the first month after the onset of symptoms failed to develop a white blood count of less than 4000 during this time and one of these had a mild persistent granulopenia. Another patient was noted to have both leukopenia and anemia in the first month of disease but is not included in the above analysis because the early data are not available. The speed with which leukopenia may develop under observation in individual cases in illustrated in fig. 8. A fifth patient (Case 26), not included on the graph, had values coinciding almost exactly with those of Case 1.

Degree of Leukopenia and Granulopenia

Counts of 2000 or less were observed in 5 of our cases during the first month after symptoms appeared; polymorphonuclear cells ranged between 530 and 1000 per cu. mm. in 6 cases, and may have been in this range in several others in which differential counts were not done. The data obtained in the Moore General Hospital on active cases before successful treatment are presented in table 6. These counts are influenced by previous treatment with blood transfusions and in many cases by inadequate antimony dosage. They indicate, however, a consistent leukopenia and granulopenia. Total counts below 1000 and polymorphonuclear counts below 500 were not observed. Acute symptomatic agranulocytosis with pharyngeal lesions was not noted in any of our cases, although it has occurred in this disease (10).

The Differential Count

Relative lymphocytosis is the rule. In only one patient (Case 12) was there absolute lymphocytosis (as high as 6800 lymphocytes per cu. mm.). This patient had marked lymphadenopathy at this time. Other patients with lymphadenopathy, however, failed to show absolute lymphocytosis.

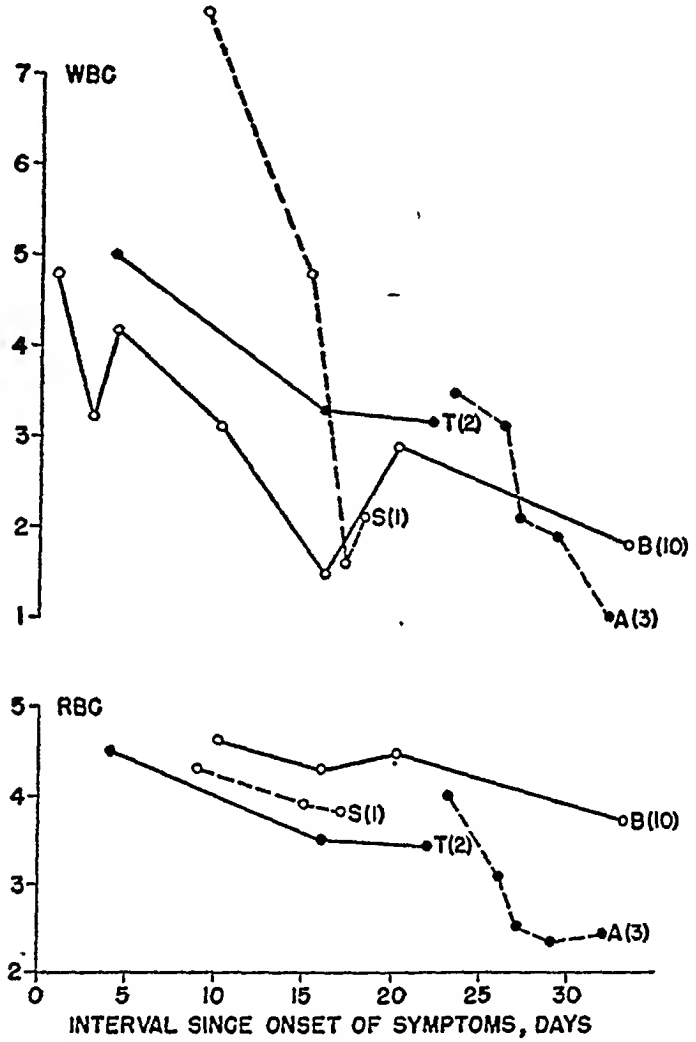


FIG. 8. EARLY CHANGES IN THE RED AND WHITE BLOOD COUNTS IN ACTIVE KALA-AZAR

Note rapid development of anemia and leucopenia in patients under observation shortly after onset of symptoms.

Large mononuclear cells were usually within the normal range, but showed a moderate relative increase in a few cases. Eosinophiles were noted in 11 cases and basophiles in 12 cases despite the paucity of white cells on the smears. These were in no instance present in greater than normal numbers.

The White Blood Count in Spontaneous Remissions and in Response to Pyogenic Infections

During spontaneous remissions of the disease the blood count reverts to or toward normal (7). There are no observations during remissions in our cases.

In 2 instances in our series, leukocytosis developed when pyogenic complications occurred (otitis media and pneumococcus pneumonia).

Speed of Development of Anemia

Of 6 cases with observations within 10 days of the onset of symptoms, none had RBC counts over 4.8 and one was below 4.0; of the five with counts greater

TABLE 6

Blood counts before and after successful treatment of leishmaniasis in Moore General Hospital

BEFORE TREATMENT									AFTER TREATMENT†					
									RBC			WBC		
Case no	Time from onset of symptoms	Previous treatment	RBC	Hbn.	Color index	WBC	Neutrophils	Platelets	3 Days	1 Week	1 Month	3 Days	1 Week	1 Month
	weeks		*millions*	*per cent*		*thousands*	*per cent*	*thousands*						
3	31	A, T	3.03	56	0.93	1.8		160	2.73	2.69	4.30	1.65	2.50	5.50
10	5	O	3.79	68	0.90	1.85	33	119	3.56	3.63	4.28	1.35	2.05	5.10
16	24	O	3.22	54	0.84	3.7			2.80	3.42	4.50	4.60	4.75	5.85
17	27	A	3.22	62	0.97	2.9	45	184		3.86			3.15	4.65
28*	7	A	2.91	48	0.83	2.05	44							
28	13	T	3.39	61	0.90	2.8	49	169	3.01	2.87	4.09	3.00	2.55	4.45
22*	16	O	2.83	55	0.96	1.75	50	82						
22	20	T	3.67	71	0.97	1.8	38	106			3.51			6.00
21	24	A	3.30	62	0.94	2.1	36	180		2.80	3.60	2.55	2.88	3.40
18	15	A	3.78	63	0.90	4.65	46		4.05	4.10		3.00	7.20	
11	19	O	3.60	77	1.07	2.9		69		3.69	3.90	3.40	2.75	5.75
23	39	A	3.62	70	0.97	3.25			3.74	3.64	4.36	6.85	6.0	
19	72	A	3.28	56	0.86	2.60			2.90	3.02	4.14	2.20	1.95	4.60
4	13	O	3.50	71	1.01	2.1	51	101		4.08	4.15	3.45	4.60	5.15
9	16	O	3.63	68	0.94	4.8	35		3.56	3.70	4.20	1.85	2.40	6.80
20	33	A	3.86	65	0.84	2.85	40	165			4.07		1.80	7.10
1	26	A	3.00	62	1.03	2.9	34	136		3.60	4.00		4.40	5.60
13	31	O	3.50	71	1.01	4.0	46	148	2.70		3.90	2.50		3.50
7	21	A	3.65	74	1.01	4.85	63	102	4.58			7.00		
6	24	A, T	3.36	65	0.97	5.7	56	148	3.35	3.3		3.90	3.40	

* Data from hospitalization immediately prior to admission to Moore General Hospital given because in these instances 2 to 4 transfusions were given shortly before transfer.

A Indicated antimony therapy. T Indicates that transfusions were given in the preceding month.

† Data presented where available at 3 ± 1 days, 7 ± 2 days and 30 ± 5 days.

than 4.0, 3 were observed to fall below 4.0 during the first month of disease, one to 2.8. Of 11 cases with initial observations between the 11th and 30th day of disease, none had RBC counts greater than 4.5 and 8 had counts of 4.0 or less; of the 3 with initial counts above 4.0, one fell to 2.8 before the end of the month, the others having no further observations during the first month. Of 9 cases with initial observation more than one month after the onset of symptoms, none had counts above 4.4 and 7 had counts below 4.0.

At the time of first observation, then, 13 of 26 cases had counts of 4.0 or less. Of 17 cases with observations during the first month after onset of symptoms, 13 fell to 4.0 or less within the month.

Degree of Anemia

In this series, considerable anemia developed fairly early in the disease but did not progress to extreme levels. Thus, of 16 cases with observations during the first month of symptoms, the median count was 3.7, the range 2.4 to 4.6. In 7 of these, lower counts were not observed prior to specific treatment. For the 28 cases as a whole the minimal pretreatment counts had a median of 3.2, a range of 2.2 to 4.5. The data on cases observed before treatment in the Moore General Hospital are recorded in Table 6. The range of these observations is 2.9 to 3.9, the median 3.4, agreeing quite closely with pretreatment levels in previous hospitalizations.

Type of Anemia

The color indices in our active cases are rarely less than 0.90, and in several instances exceed 1.00 (table 7). Hemoglobin was determined by the Sahli technique. Many observations prior to admission to Moore General Hospital are available in which the technique used is not stated. In these, as in our observations, color indices were usually between 0.90 and 1.00, rarely being below 0.85 and never below 0.82; in this group there were also a few with indices between 1.00 and 1.10. Mean corpuscular volume and mean corpuscular hemoglobin concentration were determined in 7 of our active cases (table 7). Mean corpuscular volume was above the normal average (87 cubic microns) in 6 instances and above the accepted upper limit of normal (92 cubic microns) in 4. The mean corpuscular hemoglobin concentration was below the average normal level (34 per cent) in 6 instances and below the lower limit of normal (32 per cent) in 5. It is apparent that, as a rule, there was but slight hypochromia in relation to red cell count (color index), but more marked hypochromia in relation to cell volume (mean corpuscular hemoglobin concentration). That is, the red cells were often abnormally large and pale.

Reticulocytes, icterus index, and fragility of red blood cells

Reticulocyte counts were done before treatment in 8 or our active cases. The count was 0.5 per cent or less in 6 and 1.0 and 1.4 in the other 2 cases. Normal values were likewise noted in 3 of these patients and in one other patient before admission to Moore General Hospital. Fragility of red blood cells to hypotonic saline was normal in each of 4 active cases in which it was tested. In none of the cases which were active on arrival at Moore General Hospital was the icterus index elevated above normal. The icterus index was determined early in the disease in 15 patients because of the suspicion of infectious hepatitis. These were all in the normal range except for the one patient who probably had concurrent infectious hepatitis, two who had single observations of 9 and 11 shortly after transfusions and 2 with unexplained uncorroborated single observations of 9 and 18 respectively. From these observations it is apparent that

the anemia of leishmaniasis is not hemolytic. Normoblasts were not observed in the blood smears of our patients. Metamyelocytes were present in normal numbers and no younger forms of white cells were found in the peripheral blood. These findings indicate that the changes in the blood observed in kala-aza are not characterized by excessive blood destruction or increased blood formation.

Bleeding and clotting times, platelets, calcium, fibrinogen and prothrombin time

Bleeding and clotting times were done during active disease in all but 2 cases. Bleeding times were 4 minutes or less with rare exceptions, and never exceeded 5 minutes. Clotting times were usually in the upper normal range, with none definitely abnormal. Exact timing of clot formation by the Lee-White technique was difficult since the quality of the clot was often poor, and clotting occasionally occurred on the surface while the remainder of the blood remained quite fluid

TABLE 7

Hematologic observations in active cases of kala-azar

CASE NO.	PREVIOUS TREATMENT (ANTIMONY)	TIME FROM ONSET OF SYMPTOMS	RBC	Hbn	HKT VOLUMES	COLOR INDEX	MEAN CORP. VOLUME CU MICRONS	MEAN CORP. Hbn CONC.
		weeks	*millions*	*per cent*	*per cent*			*per cent*
10	0	5	3.46	68	28	0.98	81	35.2
28	+	19	3.03	57	27	0.94	89	30.6
22	0	17	2.88	55	27	0.96	94	29.5
11	+	22	3.67	77	36	1.05	98	32.1
23	0	32	3.62	70	36	0.97	100	28.2
9	0	16	3.63	68	33	0.95	91	29.9
16	0	12	2.65	54	26	1.02	98	30.0

for as long as 10 minutes. Clot retraction was occasionally retarded, none being apparent at 2 hours in 4 instances and none at 24 hours in one patient (Case 11) in Moore General Hospital. The latter had bleeding from the gums earlier in his disease.

Platelet counts were done at some time during active disease in most of our cases. Those done before treatment in Moore General Hospital are recorded in table 6. They are uniformly subnormal, the lowest being in the case with the poorest clot retraction. Earlier observations are available in 6 of these cases. In case 23, with nosebleed at the onset of the illness, platelets were 105,000 only 12 days after the onset of symptoms; in cases (7 and 11) 132,000 and 159,000 respectively 5 and 7 weeks from the onset of symptoms; in cases 3 and 22, 70,000 and 63,000 respectively at approximately 20 weeks from onset of symptoms. Thus it is apparent that thrombocytopenia developed early and regularly in our cases but never became extreme. It seems reasonable to infer that the occasional defect in clot retraction was due to thrombocytopenia. The addition to normal blood of globulin separated from the serum of patients with kala-azar failed to prevent normal clot retraction, suggesting that hyperglobulinemia played no rôle in this defect.

Total serum calcium was in the lower normal range in our

It might be expected that an abnormally high portion of this might be bound to protein in view of the hyperglobulinemia, leaving ionized calcium subnormal. That this is not true is shown by normal values for ultrafilterable calcium in our cases.

Fibrinogen was determined in only 3 patients in our series, being normal in each instance, as in previously reported cases (15). Prothrombin time was within normal limits in each of the 4 active cases in which it was determined in Moore General Hospital. In one patient, Case 14, successfully treated before admission to Moore General Hospital, the prothrombin time was noted to be 56 per cent before treatment, with slow reversion to normal following treatment.

It is apparent that deficiency in calcium, fibrinogen or prothrombin cannot be held responsible for the bleeding observed in this disease. Thrombocytopenia occurs regularly, but is not of the degree seen in purpura. This is in keeping with previous observations, in which a lack of correlation between bleeding and platelet counts was also noted (16). Only 2 of our patients (Cases 11 and 23) had any abnormal bleeding, the former from his gums early in the disease, the latter from the nose at the onset of his disease and again during exacerbation of his disease 4 months after completion of treatment with stibanose. During this exacerbation, examination of the anterior nares revealed some area of hyperemia, superficial ulceration and crusting. The possibility must be entertained that the bleeding of kala-azar may be due at least in part to actual leishmanial lesions of the mucous membranes.

Response of blood count to treatment

Within the first week of treatment there was, in most instances, a decrease in the concentrations of circulating red and white cells. This was followed by a progressive rise which usually was well marked within one month of the start of treatment. The counts at approximately 3 days, 1 week and 1 month from onset of treatment are presented in table 6. A similar trend was apparent in cases treated before admission to Moore General Hospital in which data are available. Red cell count and hemoglobin usually became entirely normal only 3 or 4 months after start of treatment in our cases. No medication was given for the anemia *per se* in any of these cases. Platelets were followed through treatment in only one of our patients (Case 28). The pretreatment level was 169,000 with fall to 115,000 on the seventh day of treatment and return to 171,000 on the fourteenth day of treatment. This is in accord with previous observations (17). Reticulocyte counts were done at short intervals during treatment in 6 of our cases. A significant rise occurred in each instance, being manifest within 2 days after the first injection in 3 instances. The count reached 15 per cent in 2 cases. The peak occurred in approximately 2 weeks in most instances (table 8). A typical hematological response to treatment is shown in fig. 9 and a composite chart of the white counts before, during, and after treatment is shown in fig. 10. The white count in some patients rose rapidly during

TABLE 8

Reticulocyte response to specific treatment

CASE NO.	RBC BEFORE TREATMENT	RETICULOCYTES BEFORE TREATMENT	MAXIMAL RETICULOCYTE COUNT	
			Days from first injection	Level
	millions	*per cent*		*per cent*
3	3.03		13	15.0
19*(a)			13	9.4
(b)			18	3.9
(e)		1.0	27	5.3
4	3.50		7	4.6
21	3.3		18	14.8
23	3.39	0.5	15	7.0
18	3.78	0.5	15	3.4

* Response to 3 different courses of treatment. Relapse after (a) and (b); cure after (e).
(a) 10.0 Gms. neostibosan.
(b) 240 cc. stibanose.
(c) 4.0 Gms. stilbamidine.

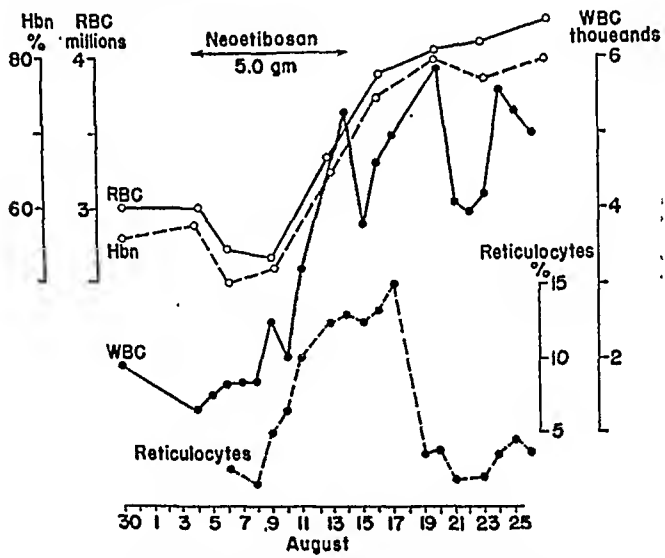


FIG. 9. HEMATOLOGIC RESPONSE TO TREATMENT
Note reticulocyte rise and reversion of RBC, WBC, and Hb. towards normal.

treatment while in others normal levels were not reached for several months. The speed of restoration of the white count to normal values is not related to the ultimate result of treatment, although persistent leucopenia for several

months after treatment should be regarded with suspicion from the standpoint of treatment failure or relapse.

Erythrocyte sedimentation rate

Regular increase in sedimentation rate in kala-azar has been described (15). This is usually so great that the cells settle out to a large degree before clotting occurs in untreated blood. In 19 of our cases, sedimentation rate was deter-

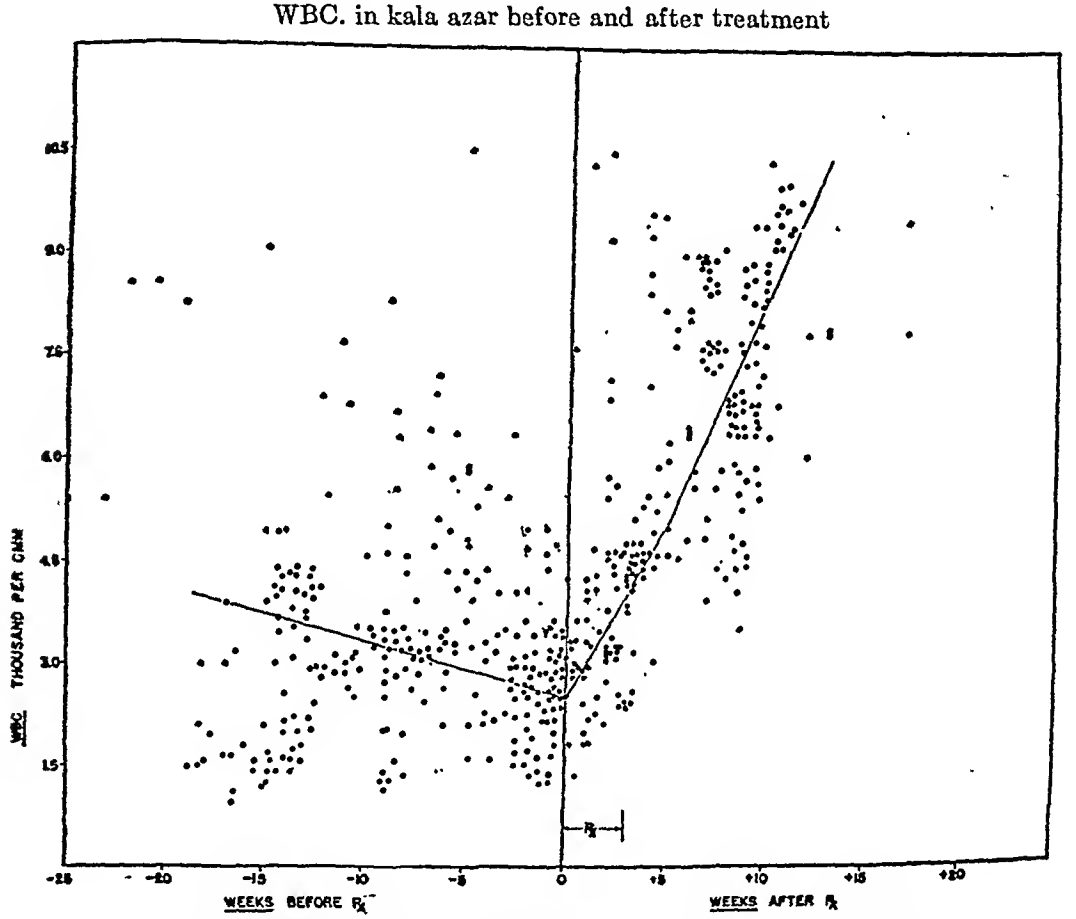


FIG. 10. WHITE BLOOD COUNTS BEFORE AND AFTER TREATMENT
Composite chart of all white counts 25 cases. Note the marked and maintained leucopenia prior to treatment and response after therapy.

mined before any specific treatment was given. The method of Wintrobe was employed in Moore General Hospital and in most of the prior determinations. One patient had sedimentation rates of 25 and 30 mm. two and three weeks after the onset of symptoms. Three others had rates of 20, 26, and 32 mm. three weeks after onset of symptoms. The remainder, observed later in the disease, had abnormal rates with 2 exceptions. The first, Case 7 had a rate of 8 mm. after 7 weeks of fever; the other, Case 13, 4 mm. per hour 32 weeks after the onset of symptoms but only 1 week after a spontaneous remission of 3 weeks' duration. It is thus apparent that the sedimentation rate is usually, but not necessarily, elevated during active disease.

Serial determinations were done during 3 treatment failures and four successful treatments. In one of the treatment failures (Case 20), the rate fell from 25 mm. before treatment to 5 mm. three weeks after completion of treatment; in the other two there was no significant change during treatment, and observations were discontinued when treatment ended. In one of the successful treatments (Case 10), the rate fell progressively from 19 to 11 mm. during treatment and to 4 mm. one month after completion of treatment. Another patient (Case 9) had a rate of 25 mm. before treatment and 9 mm. eight weeks after treatment ended. In a third patient (Case 14), the rate was 52 mm. before treatment and failed to change significantly during a course of prolonged intensive treatment. Four months from the start of treatment, however, the rate was only 4 mm. The last (Case 28), had a rate of 24 mm. before treatment; 24 and 26 mm. during treatment; and 32, 29, and 30; 1, 3, and 5 weeks respectively after completion of treatment. It is apparent from these data that the course of the sedimentation rate during treatment has no prognostic value. Thus, while a fall is noted following each of our successful treatments, it may be delayed as in Case 28, while a prompt fall to normal may occur in temporary remission, as in Case 20. The folowing instances further illustrate this fact. One patient (Case 11) had a sedimentation rate of 35 mm. before treatment with a small dose of antimony which produced a brief clinical remission. Seven weeks later, on admission to Moore General Hospital, he was febrile and splenic puncture was positive, yet the sedimentation rate was only 2 mm. per hour. Another patient (Case 23), with marked elevation of sedimentation rate, had rates of 2, 6, and 9 mm. respectively 15, 17, and 19 weeks after treatment with stibanose in Moore General Hospital. Because of failure of this patient to regain weight and strength, splenic puncture was subsequently done, yielding viable *Leishmania*. Thus, almost 5 months after treatment, it was impossible to predict activity of disease by the sedimentation rate.

Bone marrow

Bone marrow smears were examined in active cases only 4 times in this hospital. In most instances, reports on bone marrow prior to admission here note only the presence or absence of *Leishmania*. In 7 instances, however, complete descriptions of marrow are recorded. In these, as in our own examinations, marrow of average cellularity and differential count was observed. In this cellular marrow, Leishman-Donovan bodies were usually sparsely scattered.

Nature of hematological disturbance

There is no apparent hemolytic component, since red cell fragility and icterus index are normal. There is no deficiency of antianemic principle since the bono marrow is not megaloblastic, nor the anemia hyperchromic. Liver extract was used prior to admission to Moore General Hospital in several of our cases without therapeutic effectiveness. The hematological disturbance is not nutritional in the ordinary sense, since it may develop with extreme rapidity, is associated with marked leucopenia, and is characterized by only minimal hypochromia.

The peripheral blood picture is that of aplastic anemia, but the bone marrow is not morphologically aplastic. The anemia and leucopenia have been described as myelophthisic, a hypothesis which seems hardly tenable in view of the cellular marrow and relative paucity of Leishman-Donovan bodies. The picture in the periphery and in the marrow resembles that described in benzol and other poisoning (18). It seems quite possible that the anemia of kala-azar is likewise toxic either in the sense that a metabolic product of the *Leishmania* interferes with cell production or that the metabolic needs of rapidly dividing *Leishmania* or rapid formation and destruction of reticulo-endothelial cells deprives the marrow of some essential nutrients. The speed with which reticulocytosis appears when the temperature falls on institution of antimony treatment, while viable *Leishmania* are still present in abundance in spleen and marrow, is compatible with this hypothesis.

Liver function

There is no indication that liver function has suffered significantly in our cases. As has been noted previously, the icterus index was normal in all of the cases which were active on arrival in Moore General Hospital, and in almost all observations made prior to hospitalization here. Bromsulfalein excretion was studied in 6 active febrile cases, using the 5 mg. per kg. dose and the 45 minute interval. Dye retention was only 10, 10, 8, 5, 2 and 2 per cent in these cases. The cephalin flocculation was strongly positive in our cases, as was also the thymol turbidity test. This is probably not an indication of liver disease, but rather a manifestation of the marked hyperglobulinemia which characterizes the disease. As has been noted earlier, serum globulin and cephalin flocculation both reverted to normal very slowly.

In several instances, icterus index, serum bilirubin and bromsulfalein excretion were determined during and after treatment with neostibosan or with stilbamidine. In no case was there evidence of liver damage from therapy. In the patient who developed kala-azar during convalescence from apparent infectious hepatitis (Case 27), the icterus index fell from 31 to 20 in 4 days of febrile kala-azar immediately prior to treatment with antimony and fell further to 10 during the first 2 weeks of treatment. No further observations were available until admission to Moore General Hospital, three months later when the icterus index was 4.

Cold agglutinins

Agglutination of group O red blood cells in the cold by serum from patients with kala-azar has been reported.(3) Of 5 active cases tested in Moore General Hospital, 3 were negative and two were positive in low titer (1:5, 1:4).

Renal complications in Kala-azar

There were only 2 clinically important renal complications in this series. One was an instance of chronic renal insufficiency following successful treatment of kala-azar with neostibosan. This case will be discussed later. The

other, Case 23, developed classical acute glomerulonephritis approximately coincident with the onset of his kala-azar. The protocol of this case is presented in detail in the appendix. At the time of first observation, 2 weeks after the onset of symptoms, the marked leukopenia of kala-azar was already present in addition to the edema, hypertension, azotemia, albuminuria and hematuria of acute nephritis. Since leukopenia rarely develops less than 2 weeks from the onset of the symptoms of kala-azar, the latter was probably of at least 2 weeks duration. That it was not much longer than this is indicated by the fact that splenomegaly and lymphadenopathy developed under observation one week after the initial observation, and serum protein rose to 6.2 to 6.9 per cent in the first 10 days of observation, and to 10.4 two months later. There is thus good reason to believe that the nephritis began during the early clinical manifestations of kala-azar. This does not, of course, indicate a causal relationship between the 2 diseases. In fact there was marked progressive improvement in the nephritis prior to treatment of the kala-azar, with subsequent progress to probable cure, not apparently influenced by treatment. The course was not inconsistent with the natural history of the ordinary severe acute nephritis. Very few cases of acute nephritis have been reported in connection with kala-azar and these may be of an accidental association.

Of 18 cases of kala-azar active on admission to Moore General Hospital 11 had albuminuria. Two more of these had albuminuria recorded in previous hospitalizations. Of seven patients with observations prior to successful treatment given before arrival in Moore General Hospital, 3 had albuminuria. Of these 25 patients, then, 16 were observed to have albuminuria during active kala-azar. With the exception of the patient who probably had acute glomerulonephritis, albuminuria was slight (1 or 2 plus). 8 cases had microscopic hematuria on admission to Moore General Hospital and 4 more prior to arrival here. Thus 12 of the 25 cases with urine examinations done during active kala-azar were known to have microscopic hematuria. The hematuria was mild (usually reported as few or occasional RBC in centrifuged sediment). In one case, however, many RBCs were reported, and the urinary findings were so prominent that renal function tests and intravenous pyelograms were done, both proving normal. In most cases hematuria was observed on several occasions, and frequently in different installations. 5 cases had coarsely granular casts on admission to Moore General Hospital and these were noted earlier in 3 more cases. Hyaline and finely granular casts occurred somewhat more frequently. Many specimens contained 3 to 10 WBCs per HPF without relation to other urinary findings and usually without change following treatment. With the exception of the patient with probable diffuse glomerulonephritis, none of the patients with active kala-azar had hypertension, edema or azotemia, nor were they lacking in ability to concentrate urine or to excrete phenolsulfonephthalein.

Hematuria disappeared within a week of the start of treatment except in case 6 in which a few RBCs were present for the last time on the day after completion of a course of treatment lasting 22 days. Albuminuria and cylindruria usually disappeared during treatment with pentavalent antimony; rarely

albuminuria was present intermittently for a week or two after completion of treatment.

Albuminuria in our cases usually occurred during fever. It was not present regularly during pyrexia, however, and occasionally disappeared during continued high fever. Microscopic hematuria was intermittent and was likewise not strictly correlated with fever. The albuminuria of leishmaniasis has been generally attributed to fever. It seems more probable, in view of the frequency with which hematuria was observed in our cases, that it is due to focal leishmanial lesions analogous to the focal nephritis seen in bacteremias. In fatal cases, parasitized macrophages may be seen in the interstitial tissues of the kidneys (24).

One patient (Case 16) developed chronic renal insufficiency during convalescence from kala-azar, presumably from toxic effect of neostibosan. Previous data in this case are scant. Urinalysis 12 weeks from onset of symtoms of kala-azar was negative. Four weeks later 6 to 8 RBCs per HPF were reported. Five weeks after this, just prior to treatment urinalysis showed specific gravity of 1.023, no albumin, and no formed elements. No untoward reactions were noted during treatment with 3.9 Gm. of neostibosan in 23 days, and clinical response was prompt and satisfactory. Unfortunately the urine was not examined during treatment or for 10 weeks thereafter. Casual urine specimens then showed low specific gravity, and concentration tests revealed marked hyposthenuria. Excretion of phenolsulfonephthalein was only 22½ per cent in 15 minutes (normal 25 to 50 per cent), and the blood urea nitrogen was elevated to 22 mg. per cent. The urine contained no albumin or formed elements. There was no hypertension or edema, and serum albumin was normal. The patient was observed for 9½ months from the end of treatment during which time urine concentration greater than 1.015 was not attained, phenolsulfonephthalein excretion ranged between 17.5 and 20 per cent in 15 minutes, blood urea nitrogen varied between 21 and 27 mg. per cent, and urea clearance (maximal) was only 38 cc. per minute (approximately 50 per cent of normal). He remained asymptomatic except for slight nocturia, with normal blood pressure and without albumin or formed elements in the urine. There was thus in this case a diffuse non-progressive lesion with marked reduction of renal function but without signs of inflammation. This is presumably due to toxicity from antimony, though documentation is admittedly poor.

In all other cases in this series, urine examinations and renal function were normal at the end of the observation period. In most instances urine examinations were done during and shortly after treatment. As has been noted above, those patients who had albuminuria and/or hematuria cleared during treatment. Furthermore those who had negative urines before examination continued to have negative ones during and after treatment with the various pentavalent antimony preparations. Excretion of phesosulfonephthalein was determined shortly after completion of treatment in many instances and urea clearance in 4 instances; all were within normal limits. One patient (Case 19) developed slight albuminuria during treatment with stilbamidine without other

abnormality. Three consecutive specimens prior to treatment and repeated specimens after the last day of treatment were all negative. Routine urines before, during, and after treatment had specific gravity in excess of 1.024. The other patient (Case 23) who was treated with stilbamidine had slight albuminuria before treatment without appreciable change during treatment. This patient has been discussed in detail as a probable case of diffuse glomerulonephritis.

SUMMARY AND CONCLUSIONS

1. Thirty proved cases of kala-azar in American military personnel are reported. Residence in highly endemic areas and intimate contact with native quarters were largely responsible for the resulting infections.

2. The diagnosis is relatively easy to establish if one appreciates the clinical and laboratory aspects of the disease and if one is aware that it may occur in individuals long after they have been in an endemic area. In this series the delay in diagnosis was the result of unfamiliarity with the disease.

3. The principal clinical features of the disease in these cases are: (a) Acute onset by chills and fever in the majority of patients. The fever is classically intermittent and frequently two peaks occur in the daily temperature curve. Occasionally the fever at onset is sustained and in some cases after a period of active fever there is a remission followed by another period of fever. (b) Splenomegaly is marked and often develops early and rapidly. Pain and swelling in the left side of the abdomen may be an early symptom. (c) Painless lymphadenopathy without fever, splenomegaly, leucopenia, or altered serum proteins may be the only manifestation of the infection.

4. The principal laboratory findings are: (a) Leucopenia is striking and develops early. (b) The serum globulin is elevated and the serum albumen is depressed. The positive formol gel test is dependent on hyperglobulinemia as well as hypoalbuminemia. The formol gel test is not diagnostic. (c) Anemia may be severe and frequently is accompanied by moderate thrombopenia. The anemia is mildly hypochromic or normochromic. (d) The erythrocyte sedimentation rate is usually increased, but exceptions are noted. (e) Clot formation and retraction is commonly poor, presumably because of thrombopenia.

5. The most common mistakes in diagnosis are related to certain similarities between the clinical manifestations of kala-azar and malaria, undulant fever, bacteremias or septicemias, and primary diseases of the hematopoietic organs. Antimalarial drugs, sulfonamides and penicillin are of no benefit in kala-azar except to control intercurrent infections.

6. The diagnosis is established by the demonstration of *Leishmania* in smears or cultures on NNN medium from material derived from spleen, bone marrow, liver, lymph node, or peripheral blood. Smears should be searched carefully and intensively in suspected cases. Cultures should not be discarded before a month since growth in some cases may be slow. If one or more bone marrow smears or cultures are negative spleen puncture should be performed. In this

series spleen puncture was the most reliable diagnostic procedure and gave uniformly positive results.

7. The drug of choice in treatment is neostibosan. A minimum of 5.0 Gms. (0.3 Gms. intravenously daily for 17 days) should be given to patients as initial treatment or to patients who have relapsed from neostam or from smaller amounts of neostibosan. Subsequent treatment failures or relapses should be retreated with larger amounts of neostibosan (0.5 Gms. daily for 20 days). Repeated failure after several adequate courses of pentavalent antimony may occur and such cases should be treated with stilbamidine. In this series probable antimony resistance was responsible for relapse after 6 courses of antimony in one patient. Cure was accomplished with stilbamidine. Relapses in other cases were primarily the result of the use of neostam or inadequate doses of neostibosan. All patients were ultimately cured.

8. Response to adequate specific therapy is dramatic and is manifested by control of fever (1 to 2 weeks), gain in weight, restoration of the formed blood elements (1 to 2 months) and serum proteins to normal values (3 to 6 months), and recession of the spleen and liver above the costal margins (1 to 6 months).

9. Complications in American personnel are rare and consist principally of the development of intercurrent bacterial infections before or during treatment. Leucocytosis may occur in such infections. Response to chemotherapy with sufonamides or penicillin is usually satisfactory although prolonged treatment may be required.

10. Patients with kala-azar should be observed for at least 6 months after completion of treatment to discover relapses. These are usually associated with return of fever, enlargement of the spleen, leucopenia, anemia, and elevated serum globulin.

11. Kala-azar may occur in veterans a year or more after they have left endemic areas. This disease must be considered in veteran patients who present the clinical and laboratory findings discussed in this paper.

APPENDIX

Case Reports

The thirty cases of kala-azar which are the subject of this paper were studied in detail at Moore General Hospital. Some of these were initially reported to the Surgeon General in "Essential Technical Medical Data" (E. T. M. D.) from overseas theaters (19, 20). Brief clinical abstracts of our cases are presented below. The details of diagnosis, treatment, course, and laboratory findings may be found in the text and tables.

Case 1: 24 year, white, Engineer, Indian theater 16 August 1943 to April 1945, quartered in native bamboo huts. Acute onset 22 November 1944 with chills, fever, backache, pains in lower abdomen and legs. Hospitalized 29 November 1944. Liver, spleen enlarged on admission, febrile course with double daily peaks reaching 104°. WBC 7.7 on admission, 1.6 a week later. RBC 4.3 on admission, fell to 3.0 in spite of a total of 7 transfusions. Malaria smears negative; no improvement from quinine, atabrine, or sulfadiazene. Febrile course continued except for a remission of 7 days in the 5th week after onset of symp-

toms. Diagnosis in the first 2 months of disease typhus or undulant fever although malaria and amebiasis were also considered. Formol-gel negative. Sternal punctures on 7 December and 26 December negative. Leishman-Donovan bodies demonstrated in sternal marrow smears on 16 January 1945. Treatment, 3 55 grams neostibosan 18 January to 12 February 1945. Good clinical response and subsidence of fever within 9 days. Fever recurred while en route to the United States two to three months after completion of treatment. On admission to Moore General Hospital on 18 May 1945 spleen tremendously enlarged reaching well into the pelvis. Liver slightly enlarged. Fever with double peaks reaching 104°. Red count 3 million, hemoglobin 62%, white count 2.9 thousand, globulin 4.4 grams per cent, formol-gel positive, cephalin flocculation positive. Spleen puncture on 29 May 1945 positive on smear and culture. Treatment 5 grams neostibosan 31 May to 16 June 1945. Temperature became normal on 7th day of treatment. No relapse during 6 months observation after treatment. Blood count and blood proteins restored to normal although cephalin flocculation was still 2 plus at the end of 6 months. Spleen diminished progressively during observation but still palpable 1 finger breadth on discharge. It is of interest that on two occasions shortly after completion of treatment with antimony the patient suffered a relapse of *P. vivax* malaria.

Comment: Quartered in native huts. Acute onset. Spontaneous remission of fever for one week. Interval to correct diagnosis by sternal puncture two months after two prior negative punctures. Rapid development of anemia and leucopenia. Good clinical response from 3.5 grams neostibosan but relapse within 3 months. Cured by subsequent administration of 5.0 grams of neostibosan.

Case 2: 26 year old, white, Engineer, India-China Theater 10 September 1943 to 26 December 1944, quartered in native huts recently vacated by Indian Engineer troops. Acute onset 23 December 1944 with chills and fever. Hospitalized 26 December 1944. Daily intermittent chills and fever with double peaks to 105°; continuous for 15 days. Treated with quinine, atabrine, and penicillin. Recurrence of chills and fever in one month. Presumptive diagnosis recurrent malaria, liver abscess, typhus or typhoid. Continued intermittent fever without response to quinine, atabrine, sulfonamides or penicillin. Liver palpable, spleen 4 cm. below costal margin. No anemia, WBC 5.0 to 3.0, formol-gel negative. Diagnosis of kala-azar established on 12 March by demonstration of Leishman-Donovan bodies in sternal marrow smear. Treatment 2.9 grams neostibosan 13 March to 31 March. Subsidence of fever within 5 days. Liver and spleen not palpable on completion of treatment. Marked clinical improvement. No relapse during observation period of 5 months. Clinical and laboratory studies negative.

Comment: Quartered in native huts. Acute onset. Spontaneous remission for a month. Treated unsuccessfully with antimalarial drugs, sulfonamides and penicillin. No anemia and only moderate leucopenia, formol-gel negative and serum protein, normal. Interval to correct diagnosis by sternal puncture 3 months from onset. Apparent cure from very small total amount of neostibosan, usually inadequate.

Case 3: 28 year old, white, Engineer, quartered in native huts, Indian theater March 1942 until March 1945. Onset 20 November 1944 with progressive malaise, chills, fever and aches in the bones and joints. Hospitalized 12 December 1944. Liver not enlarged, spleen moderately enlarged. Intermittent daily fever with 2 to 3 chills per day. White count on admission 3.5 fell gradually to 1.0. Red blood count 2.5 million. Presumptive diagnosis kala-azar; confirmed on 21 December when *Leishmania* were demonstrated in

sternal bone marrow smears. Treatment, neostam 3.6 Gms. 22 December to 25 January. Good clinical response and subsidence of fever within 9 days. Relapse within 2 months manifested by intermittent spiking temperature reaching 104°, leucopenia (WBC 1.7), moderate anemia, (RBC 3.5). Formol-gel test positive, total proteins 9.3 Gms.%, globulin 6 Gms.%. Spleen 4 finger breadths below costal margin. Sternal marrow puncture again positive on 21 April. Retreated with neostam 4.25 Gms. from 20 April to 4 June 1945. Some clinical response again with subsidence of fever in 10 days. Within 30 days from completion of treatment white blood count was 2.5 and fever had recurred. On admission to Moore General Hospital he was found to have daily chills and fever reaching to 104°, spleen enlarged to the iliac crest, liver 4 finger breadths below the costal margin, white blood count 1.8, red blood count 3.0, hemoglobin 66%, total proteins, 8.6 Gms.%, globulin 3.9 Gms.%, formol-gel positive, cephalin flocculation positive. Platelet count 160,000. Spleen puncture on 4 August 1945 positive by smear and culture for *Leishmania*. Treatment 4 August to 15 August 1945, 5.0 Gms. of neostibosan (0.5 Gm. daily). Reticulocyte response of 13% during treatment and gradually the red count and white blood count rose to normal. Liver and spleen shrunk rapidly. No relapse during 6 months of observation.

Comment: Onset gradual becoming acute within a month. Diagnosis made by sternal puncture within two weeks after admission to the hospital. Relapse on each of two occasions after treatment with neostam. Good reticulocyte response and good clinical response and presumptive cure after 6 months observation following treatment with 5 Gms. of neostibosan given during 10 days. It is of interest that in this man's company there were two other cases of kala-azar in personnel stationed with him in the same air field in India.

Case 4: 24 year old, white, Air Force Ground Crew Engineer. India-Burma theater December 1942 to April 1945. Onset acute in the latter part of April 1945 with chills and fever while en route to the United States. Treated with quinine followed by gradual subsidence of fever. Recurrence of chills and fever on 27 May 1945 while on furlough. Hospitalized 5 June 1945. Spleen and liver found enlarged; ran daily intermittent chills and fever to 106.4°; treated with atabrine, sulfadiazene and penicillin without response. White blood count 2.0 and red blood count 2.9. Received 2 transfusions. At another hospital, fever continued; diagnosis fever of undetermined origin. Total proteins 9.8 Gms.% and globulin 5.8 Gms.%. Admitted to MGH on 27 July 1945. Complained of 20 pound weight loss from onset of illness, and daily chills and fever. Three sternal punctures at other hospitals reported negative for *Leishmania*. On admission liver 3 fingers below the costal margin and spleen well into the pelvis. White blood count 2.0, red blood count 3.5, hemoglobin 71%, platelets 100,000, globulin 3.1 Gms.%, formol-gel negative, cephalin flocculation positive, clotting time 13½ minutes. Spleen puncture on 30 July 1945 positive by smear and culture for *Leishmania*. Treatment, 200 cc of stibanose from 31 July to 9 August 1945. Good clinical response and disappearance of fever within 3 days. Rapid gain in weight followed and red count and white count gradually rose to normal. No relapse during 5 months observation. On discharge liver and spleen not palpable, red count and white count normal. Formol-gel negative but cephalin flocculation still strongly positive.

Comment: Acute onset, prolonged illness manifested by recurrent chills and fever daily for 2 months before the diagnosis of kala-azar was established by spleen puncture. Apparent cure from 200 cc. of stibanose administered during 10 days.

Case 5: 21 year old, white, Pumping Station Engineer, Indian theater. Onset 26 April with chills and fever. Hospitalized 2 May 1945. White blood count 2.0 thousand,

red blood count 4 million, hemoglobin 75%, total protein 7.5, globulin 5.8 Gms.%. Daily chills and fever reaching 103 to 105°. No response from quinine. Two sternal punctures reported negative for *Leishmania*. Sternal puncture 22 May positive by smear for *Leishmania*. Treatment 4.05 Gms. neostam, 13 May to 25 May 1945. Good clinical response and subsidence of fever within 8 days after beginning treatment. Liver and spleen receded to normal and red blood count and white blood count rose to normal. No relapse during 7 months observation. On discharge spleen 1 finger breadth below costal margin, red blood count and white blood count normal but cephalin flocculation test still positive.

Comment: Acute onset, diagnosis made within a few weeks by sternal puncture after two negative sternal punctures. Apparent cure from 4.05 Gms. neostam.

Case 6: 27 year old, colored ordnance soldier, Mediterranean theater, North Africa, Corsica, and Italy, total of 6 months. Slept in trucks and in pup tents in vicinity of native village. First hospitalized 24 August 1944 because of prolapsed hemorrhoids. During this period of hospitalization it was noted that the patient had intermittent fever with daily rises to 104° or more accompanied by chills. Treatment with quinine, atabrine, and sulfonamides had no effect on the febrile course. RBC 2.7 to 3.5 million, hemoglobin 65 to 75%, WBC 2.0 to 3.0 thousand. Further treatment with penicillin, additional sulfonamides and transfusions were not effective. Urine consistently showed the presence of albumin and a moderate number of red blood cells. Total proteins were 9.2 Gms.%. In December enlargement of the liver and spleen were noted. Fever, anemia, leukopenia as low as 1.6, albuminuria, and hyperproteinemia continued in spite of repeated antimalarial, sulfonamide, penicillin and blood transfusion therapy. On 24 November 1944 a blood smear was positive for *P. vivax* but treatment with 2.8 Gms. of quinacrine did not affect the course of the fever which remained septic with one or two rises to 104° daily. Sternal puncture on 13 December 1944 revealed no *Leishmania* on smear, but after one month's growth on N.N.N. medium characteristic leptomonads of *Leishmania* were demonstrated. Treatment, neostam, 3.5 Gms. from 28 December 1944 to 19 January 1945. Slight subsidence but not complete control of fever. Clinically there was little effect. Patient was transferred to Moore General Hospital where he was found to have continued intermittent fever and marked enlargement of the spleen and liver. RBC 3.5, hemoglobin 68%, WBC 4.7, total protein 10.7 Gms.%, globulin 7.5, formol-gel positive, cephalin flocculation positive, urine contained albumin and red cells. On 23 January 1945 splenic puncture was done and smear and culture were positive for *Leishmania*. Treatment, neostibosan 3.9 Gms., 16 February to 11 March 1945. Albuminuria and hematuria disappeared permanently shortly before completion of treatment. Fever subsided to normal before treatment was completed and did not recur during patient's observation period of approximately 8 months afterwards. The red blood count and white blood count were restored to normal within 2 months and the serum proteins within 5 months after completion of treatment. The cephalin flocculation test, however, was still positive at the end of 8 months when the patient was sent to duty.

Comment: Signs and symptoms of kala-azar discovered during a period of hospitalization for hemorrhoids. Interval to correct diagnosis by sternal puncture 4 months after discovery of fever, leucopenia, anemia and hyperproteinemia. Albuminuria and hematuria persistent throughout illness disappeared after successful specific treatment with neostibosan. Apparent cure of kala-azar from total of 3.9 Gms. of neostibosan. No relapse during period of observation of 8 months.

Case 7: 31 year old, white, AAF, service gunner, Mediterranean theater, North Africa, Sicily, Italy 29 April 1943 to 16 December 1944. Onset acute 15 September 1944 with chills

and fever. Hospitalized 15 October 1944. First white count 2,000, red count 3.1 million, formol-gel negative, serum globulin 2.9 Gms.%. Bone marrow puncture 14 November negative for *Leishmania*. Fever continued and the spleen became enlarged. While en route to United States biopsy of a rib was done and the marrow was shown to contain *Leishmania*. Fuadin was the only antimony preparation available aboard ship and consequently 30 cc. were given 4 December to 14 December. There was no apparent effect on fever from this treatment. On arrival in this country fever was present, the formol-gel test negative, serum globulin 3.4 Gms.%, WBC 2 to 4 thousand, RBC 4 million. Treated with 2.9 Gms. neostam from 1 January to 28 January 1945. Fever subsided by the end of treatment. At Moore General Hospital the patient was afebrile. Formol-gel negative, cephalin flocculation 4 plus, WBC 4 to 6 thousand, total proteins 8.4%, globulin 4.6 Gms.%. Splenic puncture on 2 March positive for *Leishmania* by smear and culture. Treatment, neostibosan 3.9 from 3 March to 26 March inclusively. Gradual restoration of serum proteins to normal, however, the cephalin flocculation test was still strongly positive 4 months after completion of treatment. Liver and spleen not enlarged, blood count entirely normal when patient was discharged to duty 5 months after completion of treatment.

Comment: Acute onset with chills and fever, formol-gel test negative in spite of elevated serum globulin, unsuccessful treatment from fuadin and 2.9 Gms. neostam. Apparent cure from 3.9 Gms. neostibosan. No relapse during 5 months after completion of treatment.

Case 8: 28 year old, colored, Quartermaster, North Africa, November 1942 to January 1943. Slept in truck frequently and had to transport natives. Italy October 1943 to March 1945. Became ill 12 January 1945 with pain on left side of abdomen. Hospitalized 19 January to 4 February 1945 with diagnosis of atypical pneumonia; x-ray of chest reported irregular areas of soft confluent linear densities in left peri-hilar area; course afebrile. Readmitted 6 February complaining of fatigability and of pain in left side of abdomen. Examination showed moderate generalized lymphadenopathy, spleen down three finger breadths and liver slightly enlarged. Afebrile. WBC 5,400 to 5,950 with only 20 to 40% neutrophils, cephalin flocculation 4 plus. Formol-gel positive. Serum proteins 10.5%. Biopsy of inguinal and epitrochlear nodes positive for L.D. bodies on 5 March. Sternal marrow positive on 12 March. Treated with 3.9 Gms. neostam, 13 March to 20 April inclusively. Irregular low grade fever during treatment; none subsequently. Sternal marrow positive again on 1 March and 1 April. Evacuated to United States apparently cured in May. Admitted to Moore General Hospital 25 May asymptomatic and afebrile. Generalized lymphadenopathy. Spleen and liver each 1 finger breadth below costal margin. WBC 4,300, RBC 3.8, hemoglobin 74%, serum albumin 3.7, globulin 6.7, formol-gel positive, splenic puncture 30 May negative, no treatment given. Convalescence uneventful. Blood count entirely normal in July, serum globulin fell gradually to 3.5 at time of discharge in September. Cephalin flocculation still positive on discharge.

Comment: Onset with pain in left side of abdomen. Early lymphadenopathy, splenomegaly, neutropenia and hyperproteinemia. Essentially afebrile course. Diagnosed by lymph node biopsy 17 days from initial hospitalization. Presumptive cure after 3.9 Gms. neostam.

Case 9: 31 year old, white, Quartermaster. North Africa 8 November 1942 to September 1943. Italy September 1943 to August 1944. Slept on ground in tents or wood huts much of the time. Secondarily infected vesicles over hands and face in August 1943, considered to originate in sand-fly bites. Developed fever and chills 24 August 1944 for which he was hospitalized on the following day. Spiking temperature to as high as 105° during first 10 days of hospitalization. WBC 3,200 on 28 August. Splenomegaly noted during first

week of hospitalization. X-ray of chest negative. Malaria smears repeatedly negative. Icterus index 3. Weakness and progressive weight loss. Spleen down 3 finger breadths, liver 1 finger breadth, in October; low-grade irregular fever during October. Several courses of antimalarial therapy without apparent effect on fever. WBC as low as 1700 with 74% lymphocytes in November with temperature rising to 101° or above. Agglutinations for typhoid negative. Heterophile antibodies absent. Blood smears, blood cultures, and marrow smears negative for leishmaniasis. Arrived in U. S. A. 4 December 1944, complaining of weakness, dull pain in left side and chilliness. Wasted. Spleen at umbilicus, liver down 2 finger breadths, both tender. Spiking fever to as high as 103°. WBC as low as 2,000, with more than 50% lymphocytes. Serum albumin 2.7, globulin 3.9. Presumptive diagnosis of leishmaniasis. Transferred to Moore General Hospital where L.D. bodies were demonstrated by splenic puncture on 19 December. Treated with 3.6 Gms. neostibosan 20 December to 10 January inclusive. Last day of fever 30 December. WBC in normal range on completion of treatment. Rapid gain weight and strength. Spleen shrunk rapidly. Proteins reverted gradually to normal before discharge on 15 May 1945.

Comment: Acute onset with fever and chills. Early splenomegaly and leucopenia. L.D. bodies demonstrated by splenic puncture after 4 months. Presumptive cure with 3.6 Gms. neostibosan.

Case 10: 28 year old, white, Air Corps Officer stationed at Headquarters, Calcutta, China-Burma-India theater from April 1943 to November 1944. Onset acute on 19 January 1945 in United States with chills, fever and headaches. Hospitalized the following day. Examination on admission not remarkable except for slight splenomegaly. Ran intermittent fever from 97 to 103° daily with one or two chills. White count 1.5 to 4.0, serum proteins normal, formol-gel test negative. Developed rapidly progressive splenomegaly and moderate anemia. Admitted to Moore General Hospital on 20 February 1945. WBC 1.8, RBC 3.7, hemoglobin 68%, platelets 118,000, serum globulin 2 Gms.%, formol-gel test negative, cephalin flocculation test positive, spleen moderately enlarged. Splenic puncture on 24 February 1945 positive by smear and culture for *Leishmania*. Treatment, neostibosan 5.1 Gms. from 25 February to 27 March 1945. Prompt subsidence of symptoms and fever within 10 days. Rapid gain in weight and restoration of white and red blood count to normal. No relapse during 4 months observation.

Comment: Acute onset in the United States several months after having left endemic area. Rapid loss of weight and marked leucopenia associated with intermittent chills and fever before the diagnosis was established by splenic puncture. Normal serum proteins and negative formol-gel test. It is of interest that one of the patient's roommates who occupied the same apartment in Calcutta also developed kala-azar. Good response and apparent cure from 5.1 Gms. neostibosan.

Case 11: 38 year old, white, Quartermaster, truck-driver, Mediterranean theater, North Africa, Sicily, and Italy 25 January 1943 to August 1944. Slept in trucks, villages, and in stables. Onset gradual in May 1944 with increasing weakness, loss of appetite, vomiting and abdominal cramps, also bleeding from the gums. Hospitalized 5 June 1944. On admission red blood count 2.5, hemoglobin 55%, WBC 1.1 to 4 thousand, platelets 130,000, sedimentation rate 30 to 50 mm. in one hour, cephalin flocculation 4 plus. Patient ran an intermittent septic fever with one or two rises daily to 103.6°. Treatment with quinine and atabrine produced no effect. Three transfusions. Liver and spleen found enlarged 2 weeks after admission and generalized lymphadenopathy also noted. Presumptive diagnoses Hodgkin's disease, lead poisoning, aplastic anemia, or Banti's syndrome. Sternal

puncture and lymph node biopsy reported negative. Serum globulin rose gradually to 6.3 Gms.% and the white count remained low. Formol-gel test positive and cephalin flocculation test positive. On August 5, 1945 bone marrow puncture done and smears reported positive for *Leishmania*. Spleen puncture done the following day also positive by smear for *Leishmania*. Lymph node previously removed was reviewed and *Leishmania* were found. An indeterminate amount of solustibosan was given during a period of 10 days with some subsidence in fever. No further supply of this drug was available and the patient was transferred to another hospital en route to this country. On arrival at Moore General Hospital on 13 September 1945 fever again marked, with one or two rises per day to 104 or 105°. WBC 2.9, RBC 2.6, hemoglobin 77%, formol-gel test positive, cephalin flocculation test positive, poor clotting of venous blood within an hour and poor clot retraction, serum globulin 3.3 Gms.%. Spleen puncture on 4 October positive by smear and culture for *Leishmania*. Treatment 15 October to 29 October 1945, neostibosan total 3.6 Gms. Midway in the course of treatment the patient coughed up rusty sputum and had an elevation of white blood count to 13,350 from a previous average level of 3 to 4 thousand. Sputum contained type 11 pneumococci and x-ray of the chest revealed left lower lobe pneumonia. One half a million units of penicillin given during the course of the next 6 days with prompt subsidence of fever. Red blood count gradually rose to normal and shortly after control of the pneumonia the white count fell to its previous level ultimately reaching normal gradually. Patient gained 25 pounds in weight, and liver and spleen gradually shrunk. Cephalin flocculation test remained positive for 3 months after completion of treatment. No relapse occurred during a period of observation after treatment of almost a year. Microscopic hematuria and albuminuria reported on numerous occasions prior to treatment; none subsequently.

Comment: Clinical findings at onset suggested various diagnoses related to the hemopoietic organs. However, all the classical clinical and laboratory findings found in kala-azar were present. Initial treatment, unfortunately, was inadequate because of unavailability of specific drugs locally. Apparent cure from a relatively small amount of neostibosan (3.6 Gms.). No relapse during a period of observation of one year. Intercurrent pneumonia during treatment during which time the white blood count rose. Prompt control of pneumonia with penicillin and falling white count to previously low level.

Case 12: 23 year old, Quartermaster truck-driver, Mediterranean theater, North Africa, Italy, Sicily from 5 April 1943 to May 1945. Onset with malaise, headaches, sore throat, nausea, vomiting, and abdominal pain on 20 December 1944. Hospitalized 26 December 1944 and found to have enlarged liver and spleen and generalized lymphadenopathy. White blood count on admission 5.4. Low grade fever was present with several remissions for about 3 months. All laboratory studies were negative except for a positive cephalin flocculation test and elevated serum globulin. Infectious mononucleosis was suspected and kala-azar was also considered but sternal puncture on 3 occasions failed to reveal any parasites. On 4 April 1945 a lymph node was removed and *Leishmania* were demonstrated. Treatment from 6 April 1945 to 13 May 1945, neostam, total 3.9 Gms. The formol-gel test was strongly positive and the serum globulin at one time as high as 10 Gms.%. However, there was no leucopenia and only slight anemia. Fever subsided by the end of treatment. The liver and spleen progressively shrunk above the costal margin and the serum globulin fell to 3.8 Gms.% during a period of 6 months. No relapse occurred during this interval of observation. Microscopic hematuria and albuminuria on several occasions early in the course of illness.

Comment: Onset simulating infectious mononucleosis. Course suggestive of leukemia or Hodgkin's disease or undulant fever. No leucopenia. Marked

elevation of serum globulin. Diagnosis established 4 months after onset by lymph node biopsy after 3 negative bone marrow punctures. Apparent cure from 3.9 Gms. neostam.

Case 13: 25 year old, white, Signal-Corps linesman. North Africa December 1942 to November 1943. Italy November 1943 to June 1944. Chills, fever, headache, weakness and anorexia led to hospitalization on 20 July 1944, shortly after return to United States for reassignment under rotation system. Sinusitis diagnosed on admission because of nasal congestion. Spiking temperature to as high as 105° during first 2 months of hospitalization; somewhat lower thereafter. Spleen down 2 finger breadths on 4 August 1944. RBC fell to 3.5, WBC to 3.3 by 3 August 1944. Malaria smears, blood cultures, chest x-ray, agglutinations, and tuberculin test all negative. Antimalarial treatment and penicillin given without effect on fever. Four blood transfusions for anemia in September. Formol-gel doubtful on 24 August, positive on 3 November. Sternal puncture 25 October reported unsatisfactory. Biopsy lymph node 18 December showed only non-specific hyperplasia. L.D. bodies found in sternal marrow 21 January 1945. At this time review of lymph node revealed L.D. bodies. Sent to Moore General Hospital for treatment. Admitted 26 February. Wasted, chronically ill. Spleen down 4 finger breadths, liver 2. Temperature rose daily to 101° to 103°. WBC 4,000, RBC 3.5. Serum albumin 4.0, globulin 5.9%. Formol-gel positive. L.D. bodies by splenic puncture 4 March 1945; transitory, mild shock and splenic pain following puncture. Neostibosan, 4.7 Gms., 5 March to 2 April inclusive. Temperature reduced after 8th treatment day, but not entirely normal until 44 days from start of treatment. Progressive gain in weight and strength and shrinking of liver and spleen. WBC rose into normal range shortly after completion of treatment. RBC rose more slowly. Serum proteins within normal limits at time of discharge, 6 September 1945, but cephalin flocculation still positive; spleen no longer palpable; weight and strength normal.

Comment: Acute onset of fever, chills and headache after leaving endemic area. Early splenomegaly and leucopenia, and marked anemia. L.D. bodies by sternal puncture after 4 months. Presumptive cure with 4.7 Gms. neostibosan.

Case 14: 24 year old, white, AAF, crew chief. India, 32 months, to October 1944. Fairly intimate contact with native laborers. Onset of chills, fever, sweats, nausea and abdominal pain 1 November 1944, while en route to United States. Went on furlough, nevertheless, until 16 December 1944, when he was hospitalized for persistence of above symptoms. Liver down 2 finger breadths, spleen, 1 or 2; RBC 3.5, WBC 2,600 on admission. Spiking temperature to 104°. Malaria smears, chest x-ray, heterophile reaction, agglutinations and blood cultures all negative. Sternal marrow negative 23 December. Splenic puncture positive for L.D. bodies and *p. vivax* on 28 December. Plasma proteins 7.2% on 1 January; formol-gel negative. Treated with 6.4 Gms. neostam followed by 2.9 Gms. neostibosan, 30 December 1944, to 15 March 1945 inclusive. Afebrile after 16 January. Splenic puncture still showed L.D. bodies on 21 February 1945, and WBC was still only 3,500 at that time. Blood count entirely normal on completion of treatment. Progressive clinical improvement. Spleen still slightly enlarged but spleen puncture on 27 April was negative by smear, culture and hamster inoculation. Serum globulin slightly elevated on discharge from Moore General Hospital, 3 June 1945. No relapse during 5 months observation after treatment.

Comment: Onset with chills, fever, sweats, nausea and abdominal pain. Diagnosis by splenic puncture on 13th day of hospitalization after previous failure by sternal puncture. Prolonged treatment with 6.4 Gms. neostam followed immediately by 2.9 Gms. neostibosan with presumptive cure.

Case 15: 29 year old, white soldier, Mediterranean theater, North Africa, Italy, and Sicily from 23 February 1943 to 22 January 1945. Onset February 1944 with abdominal pains, diarrhea, fever, chills, sweats, and weight loss. Hospitalized October 1944. Liver and spleen found enlarged, white blood count 3.2 thousand, red count 3.4 million. Formol-gel strongly positive, cysts of *E. histolytica* present in the stool. Urine contained albumin. There was moderate intermittent fever. It was suspected that the patient had a urinary tract infection or amoebiasis. However, kala-azar was also considered because of anemia, leucopenia and enlargement of the liver and spleen. On 27 October a sternal bone marrow puncture was done and *Leishmania* were demonstrated in the smear. Neostam, total 3.9 Gms. were given from 27 October to 16 November 1944. 2.4 million units of penicillin were given after completion of the neostam treatments. Serum globulin was 7 Gms.% and the cephalin flocculation test strongly positive. The red count and white count were restored to normal and within 2 weeks of treatment temperature was normal and remained so. There were scaly pigmented lesions over both shoulders, which were suspected of possibly being due to leishmaniasis but smears and cultures as well as Hamster inoculation from the skin were negative. The cephalin flocculation test became negative after 4 months and within 6 months the serum proteins were restored to normal. Relapse did not occur during a period of observation of almost a year after completion of treatment.

Comment: The diagnosis of kala-azar was established in this case within 3 weeks of hospitalization. Apparent cure resulted from 3.9 Gms. neostam. The presence of cysts of *E. histolytica* in the stool and albumin in the urine suggested originally amoebiasis or a urinary tract infection as diagnoses.

Case 16: 35 year old, colored, Quartermaster truck-driver, Mediterranean theater' North Africa, and Sicily May 1943 until April 1944. Frequently slept in trucks and quartered in tents in vicinity of native villages. Onset with chills and fever 25 May 1944 more than a month after arrival in this country. In spite of recurrent fever and weight loss he remained on duty until 21 August 1944 when he was hospitalized. In the hospital he ran a continuous intermittent fever with one or two peaks to 102° daily. Red blood count on admission 2.9, WBC 3.5, hemoglobin 54%, sedimentation rate 35 mm. in one hour, serum globulin 5.1 Gms.%, formol-gel test positive. Spleen found enlarged by x-ray of the abdomen. Kala-azar was suspected but a sternal puncture on 29 December 1944 was negative. The patient was transferred to Moore General Hospital on 7 November 1944 with a diagnosis of fever of unknown origin. RBC on admission 3.2, hemoglobin 54%, WBC 3.7, serum globulin 6.2, cephalin flocculation strongly positive. Spleen puncture on 14 November 1944 positive by smear and culture for *Leishmania*. Treatment, 15 November 1944 to 8 December 1944, neostibosan 3.9 Gms. Temperature became normal within 4 days after beginning treatment. Ten weeks following completion of treatment it was noted that the urine had a fixed specific gravity; blood urea nitrogen 21.8, and PSP excretion 17.5% in 15 minutes. Within several months the serum protein became normal. The red blood count and white blood count rose to normal and the liver and spleen were no longer palpable. However, during a period of observation of more than 6 months, hyposthenuria continued unchanged and blood urea nitrogen remained elevated. There was no hypertension and no proteinuria. Microscopic examination of the urine was normal. It was felt that this patient developed a kidney lesion as a result of treatment with pentavalent antimony. Relapse from kala-azar did not occur during a period of observation of almost a year. The patient received a medical discharge for disability.

Comment: Onset in this country more than a month after leaving endemic area. Diagnosis of kala-azar not made until 6 months after onset of illness. All the classical, clinical and laboratory signs were present in this case. Development of a renal lesion following treatment with antimony.

Case 17: 25 year old, white, Ground Crew Mechanic Air Corps, Indian theater approximately 15 months. Onset 15 November 1944 with headache, chill, fever and sweats. Hospitalized 28 November 1944. Remained 44 days at the end of which time without specific therapy the temperature subsided spontaneously. Fever recurred 7 days after discharge and patient re-hospitalized. At this time the liver and spleen were found to be enlarged. There were one or two daily rises to as high as 104.8°. White blood count 3.2, red blood count 3.8, formol-gel negative. Sternal puncture on 20 January 1945 positive by smear for *Leishmania*. Treatment, 22 January 1945 to 25 February 1945 total 4.7 Gms. neostam. Temperature returned to normal approximately two weeks after beginning treatment. The white count at this time was 3.5. The spleen had become larger. The red blood count 3.5. Retreated with neostibosan 21 March 1945 through 7 April 1945, total 2.4 Gms. Temperature subsided but on arrival in this country in May 1945 fever had recurred. On admission to Moore General Hospital the spleen and liver were found tremendously enlarged, cephalin flocculation test strongly positive, the white blood count 3.2 to 2.9, and the red count 3.4. Serum globulin was 2.9 to 3.1. Splenic puncture on 27 May 1945 positive for *Leishmania* by smear and culture. Treatment 5.0 Gms. neostibosan from 28 May 1945 to 12 June. The temperature which had spiked to 104 or 105° once or twice daily became normal when treatment was completed. There was gradual restoration of the red and white blood counts to normal and the liver and spleen shrunk above the costal margin. No relapse during next 6 months. On discharge the red and white counts were normal. The cephalin flocculation was negative and the serum proteins normal.

Comment: Onset with chills and fever lasting 44 days then spontaneous remission without treatment. Relapse after initial treatment with 4.7 Gms. neostam and relapse again after retreatment with neostibosan 2.4 Gms. Apparent cure after 5 Gms. of neostibosan. The formol-gel test in this case was only doubtful and serum globulin never very high.

Case 18: 27 year old, colored, truck driver, North Africa and Italy. Mild malaise, fever, headache and anorexia starting 7 July 1945 increasing progressively to hospitalization on 11 July. Examination negative. Spiking undulating fever reaching as high as 103.8. Blood culture, malaria smears and chest film negative. WBC 4,650 on admission, 3,200 3 weeks later, 2,200 on 3 September. Kahn negative on admission; later weakly positive; later still strongly positive. Generalized lymphadenopathy noted on 18 August 1945, spleen noted 2 finger breadths below costal margin at same time. L.D. bodies found in sternal marrow 25 August. Treated with 4.0 Gms. neostam 5 September to 3 October inclusively. Otitis media, left, treated with penicillin 25,000 units q. 3 hr. 14 to 29 September inclusively. General condition improved during treatment but fever continued. Spleen no longer palpable on 25 September 1945. Right otitis media 15 October 1945 treated with penicillin. Evacuated by air to U. S. arriving at Moore General Hospital 26 October 1945 with only complaint of pain and discharge in right ear. Examination showed right otitis media and firm, non-tender 1 cm. nodes in axillary, epitrochlear and inguinal regions. WBC 4,650, RBC 3.8, serum albumin 4.3, globulin 4.8, formol-gel positive, Kahn doubtful positive, temperature rise to 101 and 102° daily for 6 days. Given 160,000 units of penicillin daily from 1 to 7 November inclusively. Temperature fell into the normal range during this course but rose again on its termination in spite of cessation of aural discharge. Sternal marrow positive for L.D. bodies 8 November. Given 5.0 Gms. neostibosan 13 to 22 November inclusively. On 7th day of this treatment he developed high fever, chest pain and cough promptly relieved by 720,000 units of penicillin given between 20 and 24 November inclusive. On 26 November fever, pain and cough recurred and he was given 1,600,000 units of penicillin between 26 November and 3 December with sustained relief. The WBC rose to as high as 8,800 during the pneumonia and was 5,500 to 6,400 during the first 3 days of December. Went on furlough 14 December and while at home

Case 15: 29 year old, white soldier, Mediterranean theater, North Africa, Italy, and Sicily from 23 February 1943 to 22 January 1945. Onset February 1944 with abdominal pains, diarrhea, fever, chills, sweats, and weight loss. Hospitalized October 1944. Liver and spleen found enlarged, white blood count 3.2 thousand, red count 3.4 million. Formol-gel strongly positive, cysts of *E. histolytica* present in the stool. Urine contained albumin. There was moderate intermittent fever. It was suspected that the patient had a urinary tract infection or amoebiasis. However, kala-azar was also considered because of anemia, leucopenia and enlargement of the liver and spleen. On 27 October a sternal bone marrow puncture was done and *Leishmania* were demonstrated in the smear. Neostam, total 3.9 Gms. were given from 27 October to 16 November 1944. 2.4 million units of penicillin were given after completion of the neostam treatments. Serum globulin was 7 Gms.% and the cephalin flocculation test strongly positive. The red count and white count were restored to normal and within 2 weeks of treatment temperature was normal and remained so. There were scaly pigmented lesions over both shoulders, which were suspected of possibly being due to leishmaniasis but smears and cultures as well as Hamster inoculation from the skin were negative. The cephalin flocculation test became negative after 4 months and within 6 months the serum proteins were restored to normal. Relapse did not occur during a period of observation of almost a year after completion of treatment.

Comment: The diagnosis of kala-azar was established in this case within 3 weeks of hospitalization. Apparent cure resulted from 3.9 Gms. neostam. The presence of cysts of *E. histolytica* in the stool and albumin in the urine suggested originally amoebiasis or a urinary tract infection as diagnoses.

Case 16: 35 year old, colored, Quartermaster truck-driver, Mediterranean theater' North Africa, and Sicily May 1943 until April 1944. Frequently slept in trucks and quartered in tents in vicinity of native villages. Onset with chills and fever 25 May 1944 more than a month after arrival in this country. In spite of recurrent fever and weight loss he remained on duty until 21 August 1944 when he was hospitalized. In the hospital he ran a continuous intermittent fever with one or two peaks to 102° daily. Red blood count on admission 2.9, WBC 3.5, hemoglobin 54%, sedimentation rate 35 mm. in one hour, serum globulin 5.1 Gms.%, formol-gel test positive. Spleen found enlarged by x-ray of the abdomen. Kala-azar was suspected but a sternal puncture on 29 December 1944 was negative. The patient was transferred to Moore General Hospital on 7 November 1944 with a diagnosis of fever of unknown origin. RBC on admission 3.2, hemoglobin 54%, WBC 3.7, serum globulin 6.2, cephalin flocculation strongly positive. Spleen puncture on 14 November 1944 positive by smear and culture for *Leishmania*. Treatment, 15 November 1944 to 8 December 1944, neostibosan 3.9 Gms. Temperature became normal within 4 days after beginning treatment. Ten weeks following completion of treatment it was noted that the urine had a fixed specific gravity; blood urea nitrogen 21.8, and PSP excretion 17.5% in 15 minutes. Within several months the serum protein became normal. The red blood count and white blood count rose to normal and the liver and spleen were no longer palpable. However, during a period of observation of more than 6 months, hyposthenuria continued unchanged and blood urea nitrogen remained elevated. There was no hypertension and no proteinuria. Microscopic examination of the urine was normal. It was felt that this patient developed a kidney lesion as a result of treatment with pentavalent antimony. Relapse from kala-azar did not occur during a period of observation of almost a year. The patient received a medical discharge for disability.

Comment: Onset in this country more than a month after leaving endemic area. Diagnosis of kala-azar not made until 6 months after onset of illness. All the classical, clinical and laboratory signs were present in this case. Development of a renal lesion following treatment with antimony.

Case 17: 25 year old, white, Ground Crew Mechanic Air Corps, Indian theater approximately 15 months. Onset 15 November 1944 with headache, chill, fever and sweats. Hospitalized 28 November 1944. Remained 44 days at the end of which time without specific therapy the temperature subsided spontaneously. Fever recurred 7 days after discharge and patient re-hospitalized. At this time the liver and spleen were found to be enlarged. There were one or two daily rises to as high as 104.8°. White blood count 3.2, red blood count 3.8, formol-gel negative. Sternal puncture on 20 January 1945 positive by smear for *Leishmania*. Treatment, 22 January 1945 to 25 February 1945 total 4.7 Gms. neostam. Temperature returned to normal approximately two weeks after beginning treatment. The white count at this time was 3.5. The spleen had become larger. The red blood count 3.5. Retreated with neostibosan 21 March 1945 through 7 April 1945, total 2.4 Gms. Temperature subsided but on arrival in this country in May 1945 fever had recurred. On admission to Moore General Hospital the spleen and liver were found tremendously enlarged, cephalin flocculation test strongly positive, the white blood count 3.2 to 2.9, and the red count 3.4. Serum globulin was 2.9 to 3.1. Splenic puncture on 27 May 1945 positive for *Leishmania* by smear and culture. Treatment 5.0 Gms. neostibosan from 28 May 1945 to 12 June. The temperature which had spiked to 104 or 105° once or twice daily became normal when treatment was completed. There was gradual restoration of the red and white blood counts to normal and the liver and spleen shrunk above the costal margin. No relapse during next 6 months. On discharge the red and white counts were normal. The cephalin flocculation was negative and the serum proteins normal.

Comment: Onset with chills and fever lasting 44 days then spontaneous remission without treatment. Relapse after initial treatment with 4.7 Gms. neostam and relapse again after retreatment with neostibosan 2.4 Gms. Apparent cure after 5 Gms. of neostibosan. The formol-gel test in this case was only doubtful and serum globulin never very high.

Case 18: 27 year old, colored, truck driver, North Africa and Italy. Mild malaise, fever, headache and anorexia starting 7 July 1945 increasing progressively to hospitalization on 11 July. Examination negative. Spiking undulating fever reaching as high as 103.8. Blood culture, malaria smears and chest film negative. WBC 4,650 on admission, 3,200 3 weeks later, 2,200 on 3 September. Kahn negative on admission; later weakly positive; later still strongly positive. Generalized lymphadenopathy noted on 18 August 1945, spleen noted 2 finger breadths below costal margin at same time. L.D. bodies found in sternal marrow 25 August. Treated with 4.0 Gms. neostam 5 September to 3 October inclusively. Otitis media, left, treated with penicillin 25,000 units q. 3 hr. 14 to 29 September inclusively. General condition improved during treatment but fever continued. Spleen no longer palpable on 25 September 1945. Right otitis media 15 October 1945 treated with penicillin. Evacuated by air to U. S. arriving at Moore General Hospital 26 October 1945 with only complaint of pain and discharge in right ear. Examination showed right otitis media and firm, non-tender 1 cm. nodes in axillary, epitrochlear and inguinal regions. WBC 4,650, RBC 3.8, serum albumin 4.3, globulin 4.8, formol-gel positive, Kahn doubtful positive, temperature rise to 101 and 102° daily for 6 days. Given 160,000 units of penicillin daily from 1 to 7 November inclusively. Temperature fell into the normal range during this course but rose again on its termination in spite of cessation of aural discharge. Sternal marrow positive for L.D. bodies 8 November. Given 5.0 Gms. neostibosan 13 to 22 November inclusively. On 7th day of this treatment he developed high fever, chest pain and cough promptly relieved by 720,000 units of penicillin given between 20 and 24 November inclusive. On 26 November fever, pain and cough recurred and he was given 1,600,000 units of penicillin between 26 November and 3 December with sustained relief. The WBC rose to as high as 8,800 during the pneumonia and was 5,500 to 6,400 during the first 3 days of December. Went on furlough 14 December and while at home

again developed pneumonia for which he was hospitalized and treated with penicillin. Further convalescence was uneventful. On the possibility that he had had primary syphilis at the time of initial hospitalization, he was given 2,400,000 units of penicillin in 7½ days before being returned to duty.

Comment: Acute onset with fever, malaise, headache, and anorexia. Diagnosis established by sternal puncture 44 days after hospitalization. Treatment failure with 4.0 Gms. neostam. Subsequent apparent cure with 5.0 Gms. neostibosan. Pretreatment course complicated by purulent otitis media and pneumonia both responding to penicillin promptly but requiring unusually prolonged therapy for ultimate cure.

Case 19: 27 year old, white, file clerk, Indian theater 17 May 1942 to 25 August 1944. Intimate contact with native quarters and villages. Onset acute 18 August 1944 with chills, fever, generalized aching and headache. Hospitalized 25 August. One or two temperature rises daily with chills. Treatment with quinine, atabrine, sulfonamides, and penicillin had no clinical effect on fever or symptoms. Physical examination negative except for enlargement of spleen discovered by x-ray of abdomen. WBC 5,200 on admission fell gradually and remained between 2 and 3 thousand subsequently. RBC 2.8, hemoglobin 60%. Formol-gel tests during first 4 months of illness negative. On 29 December serum albumin 2.7, globulin 4.1 Gms.%. Presumptive diagnoses during first 4 months of illness were dengue, malaria, amebiasis, and finally unexplained fever. On 30 December 1944 smears from sternal marrow positive for *Leishmania*. Treatment as follows: fuadin, 42.5 cc. (30 December 1944 to 20 January 1945), no effect on fever, anemia, and leucopenia. Neostibosan, 2.7 Gms. (5 February to 24 February 1945), good response, clinically and cessation of fever for one month. Relapse on 29 March 1945 manifested by recurrence of fever. Anemia, leucopenia and splenomegaly persisted. Neostam 0.75 Gm. (31 March to 14 April 1945). Temporary slight lowering of fever but no clinical effect and no change in blood picture. Evacuated to United States arriving at Moore General Hospital 6 May 1945. Spleen 8 finger breadths below left costal margin. One or two rises in temperature daily to 104 to 105.6°. RBC 2.9, hemoglobin 65%, WBC 1.8. Serum albumin 3.0 and globulin 6.6 Gms.%, formol-gel and cephalin flocculation positive. Platelets 134,000. Spleen puncture 17 May 1945 positive by smear and culture for *Leishmania*. Treatment 17 May to 4 June 1945 neostibosan 5.0 Gms. Temperature became normal on 15th day of treatment. Spleen receded somewhat. RBC 3.2, WBC 3.9. Returned from one month furlough with history of chills and fever and weight loss while at home. The spleen had enlarged and fever was present as previously. Spleen puncture again positive. Treatment, stibanose 240 cc. from 6 August to 16 August 1945. Temperature became normal 1 day after completion of treatment. Reticulocytosis 9.4%, RBC rose to 3.9 and WBC to 4.9. Patient asymptomatic and again given a 30 day furlough. Chills and fever recurred and on readmission spleen found to be still larger. RBC 2.8, WBC 2.8, serum globulin 6.6. Spleen puncture 21 August 1945 again positive by smear and culture. Treatment 10.0 Gms. neostibosan from 24 October to 12 November. Prompt control of fever. Reticulocytosis 13.9% on last day of treatment. Relapsed within a month at which time spleen was well into the pelvis and WBC 2.6. Fever had recurred. Spleen puncture 10 January 1946 again positive. Treatment stilbamadine 4.1 Gms. from 12 January 1946 to 2 February 1946. Fever controlled before completion of treatment. Reticulocytosis 5.3%. Gradual rise of RBC to 4.74 million and WBC to 7.4 22 days after completion of treatment. Spleen enlarged during early part of treatment but by 15th day after treatment was only 3 finger breadths below left costal margin. Continued observation for 5 months without relapse.

Comment: Acute onset. Interval to correct diagnosis by sternal puncture 4 months from onset. Initial treatment with fuadin ineffective; subsequent

good or slight clinical response from each of several courses of antimony. Relapse after ordinarily curative amounts of antimony on each of 3 occasions i.e. 5.0 Gms. neostibosan, 240 cc stibanose, and 10 Gms. neostibosan. Apparent cure from 4 Gms. stilbamidine. Probable development of antimony resistant strain of *Leishmania* following repeated courses of non-curative amounts of antimony early in the disease.

Case 20: 28 year old, white, AAF, Indian theater 30 November 1942 to October 1944. Lived in building with bamboo walls and thatched roof. Abrupt onset of generalized aching and slight headache 5 October 1944. Temperature elevated. In sick bay 10 days, then to duty. Four days later recurrence of aching, now more severe. Hospitalized 19 October 1944. Spleen palpable on admission. Temperature rose to as high as 104° during first week of hospitalization and 100 to 101° daily thereafter until specific treatment was started. Many days with double temperature peaks and some with triple ones. Fever, chills, and one epistaxis. Working diagnoses malaria, dengue, hepatitis and leishmaniasis. L.D. bodies found in smear from sternal puncture 22 December 1944. At this time spleen palpable just at costal margin; liver 2 finger breadths below costal margin. WBC had fallen to 2,550 and RBC to 3.6 from 5,900 and 4.6 respectively on admission. Serum albumin was 3.8, globulin 3.7, formol-gel negative. Treated with 4.60 Gms. neostam 22 December to 31 January inclusively. The temperature continued to rise to or near 100° daily during treatment being usually between 99 and 100° during the last two weeks of treatment, and below 99 immediately after completion of treatment. Symptomatic improvement with weight gain, but liver and spleen remained enlarged and WBC failed to rise above 5,000. Evacuated to United States 3 April 1945. Admitted to Moore General Hospital after furlough on 23 June 1945. Chronically ill. Liver just palpable, spleen at the level of umbilicus. Temperature rose to and above 100° daily. RBC 3.9, WBC 2,850, serum albumin 3.9, globulin 4.5, formol-gel positive. L.D. bodies found by splenic puncture 25 June 1945. Treated with 5.0 Gms. neostibosan 27 June to 13 July inclusively. On the 5th day of treatment the temperature failed to rise above 99° and subsequent course was continuously [illegible] ght and strength. Spleen shrunk rapidly. [illegible] treatment. Discharged to duty 15 Novem- [illegible] ount and serum protein within normal range. Cephalin flocculation still three plus on discharge.

Comment: Abrupt onset with generalized aching, headache, and fever. Diagnosis made by sternal puncture 65 days after hospitalization. Treatment failure with 3.65 Gms. neostam. Subsequent presumptive cure with 5.0 Gms. neostibosan. Proteins within normal range but cephalin flocculation still positive on discharge.

Case 21: 24 year old, colored, welder, AAF, North Africa from October 1944 to February 1945. Slept on ground in tents. Developed slight evening headache and chilliness 4 February 1945. To sick call 7 February; temperature 101°; hospitalized same day. Spiking fever, splenomegaly, mild anemia and leucopenia and loss of weight (20 pounds in 6 weeks). Malaria and miliary tuberculosis considered but blood smears and chest films negative. Penicillin given without effect. L.D. bodies seen in blood smear on 25 March and confirmed by sternal marrow examination on 12 April. Given 4.48 Gms. neostam 13 to 21 April inclusively; nausea, vomiting, chill and fever, after each of the first 5 injections; fever subsided shortly before the end of treatment. Weight and strength increased; WBC rose from 3,000 to 5,400, hemoglobin from 7.2 to 10.5 Gms. Spleen still palpable when returned to duty on 5 May. Two weeks later fever, chills, and headache recurred. Rehospitalized 6 June 1945; spleen palpable; low grade fever; hemoglobin 75%; RBC 3.6;

WBC 6,100; formol-gel positive. Sternal marrow on 11 June showed L.D. bodies. Evacuated to United States without further treatment. Admitted to Moore General Hospital 27 July 1945. Examination negative except for spleen two finger breadths below costal margin; low grade fever; anemia, leucopenia, hyperglobulinemia, positive formol-gel and cephalin flocculation. L.D. bodies demonstrated by splenic puncture 15 September. Treated with 200 cc. stibanose 16 to 27 September inclusively. Irregularly febrile during treatment with considerable pain in splenic area during this period. No fever after 10th day of treatment. Blood count normal by the end of November. Serum globulin did not fall significantly during the first 3 months after treatment but then fell from 5.3 to 4.4 in the last two months. Stamina subnormal through January 1946 but excellent thereafter. Discharged to duty on 22 April.

Comment: Abrupt onset with headache, chilliness, and fever. L.D. bodies seen in blood smear 46 days after hospitalization. Treatment failure with 4.48 Gms. neostam. Retreated with 200 cc. stibanose with prompt control of fever but equivocal gain in strength until 3 months after completion of treatment, following which rapid return to normal. Fall in serum globulin correspondingly delayed.

Case 22: 23 year old, white, carpenter, Mediterranean theater, North Africa, and Italy 13 May 1943 to 24 March 1945. Onset December 1944 was gradual with progressive enlargement of the abdomen, pallor, and later in January chills, fever, sweats and progressive loss of weight. Hospitalized 16 February 1945. On admission liver and spleen were each found enlarged 4 finger breadths below costal margin. Generalized lymphadenopathy present; white count 3.3, cephalin flocculation positive. Presumptive diagnoses Hodgkin's disease or aleukemic leukemia. Several bone marrow examinations were made to study the leucopenia but nothing was found. Likewise a lymph node was removed and showed nothing specific. The liver and spleen increased progressively and fever was hectic, consisting of one or two chills per day with rises to as high as 105°. Globulin was elevated to 5 Gms.% and formol-gel test was positive. Kala-azar was suspected but again another lymph node biopsy and sternal marrow puncture were negative for Leishman-Donovan bodies. The white count ranged between 1 and 2 thousand and the red count fell progressively to about 2 million. Patient arrived at Moore General Hospital on 10 May 1945 with a transfer diagnosis of aleukemic leukemia. The red count was 3.6 and the white count 1.8. Formol-gel and cephalin flocculation tests both strongly positive. Serum globulin 4.6 Gms.%, clotting time 16 minutes (Lee and White method), the liver and spleen were both tremendously enlarged and the patient showed evidence of marked cachexia. There was generalized lymphadenopathy and the fever course during the first few days of observation was as previously described; namely, intermittency with one or two peaks per day rising to 104 or 105°. Spleen puncture was performed on 14 May 1945 and *Leishmania* were demonstrated by smear and culture. Treatment was begun on the following day consisting of neostibosan, a total of 5 Gms. being given from 15 May to 1 June. The temperature subsided within 10 days and for the first time in 5 months this patient was free of fever. There was a striking increase in appetite and the patient gained approximately 30 pounds during a month. The spleen and liver shrunk very rapidly so that within a month of completion of treatment the spleen and liver were barely palpable. There was progressive rise in the red and white count so that within several months it was normal. No relapse occurred during seven months observation and when the patient was discharged his liver and spleen were no longer palpable, the serum proteins were normal, the red and white counts were normal and the cephalin flocculation test was negative. Microscopic hematuria and albuminuria observed repeatedly, clearing after successful therapy.

Comment: Onset gradual for a month becoming acute, manifested by enlargement of the abdomen, chills and fever. When first seen the prominent features

were leucopenia, large liver and spleen, and adenopathy as well as fever. For several months the presumptive diagnoses were Hodgkin's disease or aleukemic leukemia. Several attempts at diagnosis by bone marrow and lymph node examination were unsuccessful. The diagnosis was established by spleen puncture 5 months after onset of patient's illness. There was a striking and dramatic response to 5 Gms. of neostibosan and no relapse occurred during more than 6 months observation.

Case 23: 36 year old, colored, Quartermaster ration dump worker. North Africa and Italy. Scarlet fever in childhood; bed ridden 6 months; nature of complication unknown. While in service, general health excellent until 10 June 1945 when he was hospitalized with a 5 day history of shortness of breath, dragging sensation in abdomen and swelling of legs. He had had a productive cough for one week and daily nose bleeds for two weeks. Examination revealed soft systolic mitral murmur, BP 155/95, rales at lung bases and edema of legs. WBC 2,750. Urine contained RBC's, WBC's and casts. Improved in 10 days and transferred to another installation 20 June where he was still dyspneic on exertion; BP 142/92 to 180/108; RBC 3.0 with proportional reduction in hemoglobin; WBC 5,400 to 5,000; RBC's, WBC's and casts in urine; serum albumin 3.2, globulin 3.7 on 25 June; NPN 54 mg. per cent. Intermittent, irregular low grade fever. Improved with rest and transfusions and evacuated to United States where he was hospitalized on 15 August with diagnosis of chronic glomerulonephritis; systolic apical murmur still present; BP 132/86; mild generalized adenopathy. RBC 3.0; WBC 3.6; NPN 41 mg. per cent; serum albumin 3.8, globulin 6 6; urine showed RBC's, WBC's and casts, sternal puncture done on 25 September to investigate blood dyscrasia revealed L.D. bodies on smear. Transferred to Moore General Hospital for treatment 4 October 1946. Previous findings confirmed. BP 140/96, B.U.N. 15 mg. per cent. Treated with 200 cc. stibanose, 22 October to 1 November 1945. Essentially afebrile course. On return from convalescent furlough 26 January 1946 there was intermittent irregular low grade fever and the spleen was still down 2 finger breadths; B.U.N. 12; RBC 2.7; WBC 4,350; serum albumin 3 1; globulin 6.1. During the next month, the weight fell 5 pounds and sternal puncture on 1 March was positive for L.D. bodies. Treated with 4.0 Gms. stilbamidine, 18 March to 7 April, without untoward effect except mild local phlebitis and transitory flushing and tingling during injections. WBC rose from 3,250 to 6,000 during treatment. Excretion of BSP and PSP both normal at end of treatment. Asymptomatic on return from furlough 29 April; WBC 5,900; RBC 4.2; hemoglobin 82 per cent; serum albumin 3.5, globulin 4.7. Went on furlough again, returning 23 May with fever, chills, genital lesion, marked inguinal adenopathy; WBC 8,200; Frei test strongly positive. Fever subsided during treatment with sulfathiazole, but RBC and hemoglobin fell and serum globulin rose again following this episode. Subsequent convalescence uneventful, with disappearance of all evidences of nephritis.

Comment: Onset of illness with acute nephritis. Diagnosis of leishmaniasis made by sternal marrow examination done to attempt to explain leucopenia in nephritis. Treatment failure with 200 cc stibanose. Cure after 4.0 Gms. stilbamidine. Lymphogranuloma inguinale during convalescence with resulting acute fall in hemoglobin and rise in globulin.

Case 24: 24 year old, white, Engineer, India. Developed chills, fever, low back ache, retrobulbar headache and easy fatigability on 1 May 1945, but continued on duty until 14 May when he suddenly lost consciousness for a few minutes. Hospitalized on this day; physical examination negative but there was spiking fever. Malaria smears and agglutinations were negative. Febrile course continued with WBC 4 to 6 thousand. Palpable spleen first noted 7 June. Transferred to general hospital with fever of unknown origin 10 June; examination negative except for palpable spleen; spiking fever continued; WBC

4,300 on admission falling to 2,950 on 16 June and 2,300 a week later. Leishmaniasis was suspected but sternal punctures were negative on 25 and 28 June. Formol-gel positive 27 June and a third sternal marrow on 5 July revealed L.D. bodies on smear. Serum albumin 3.1, globulin 4.6. Spleen enlarged gradually during this period to reach well below the umbilicus. Treated with 3.8 Gms. neostam 8 to 31 July inclusively. Temperature was normal from the fifth day of treatment. The spleen receded during treatment and the WBC was normal at the end of treatment. The weight which fell from 150 to 123 before treatment began to rise and symptoms were entirely lacking. RBC and hemoglobin normal on 5 September 1945. On admission to Moore General Hospital he was asymptomatic and weighed 142 pounds. Examination was negative except that spleen was palpable 3 finger breadths below costal margin. Blood count was normal, serum albumin 4.5, globulin 3.8, cephalin flocculation 3 plus, thymol turbidity 6.5 units. Sternal puncture negative. Spleen shrunk gradually but was still palpable at 1 finger breadth below costal margin on discharge 15 March 1946. At the time serum globulin had fallen to 2.4%, thymol turbidity to 3.1 units and the cephalin flocculation was negative.

Comment: Acute onset with chills, fever, headache, backache and fatiguability. Third sternal puncture 52 days after hospitalization showed L. D. bodies. Presumptive cure after 3.8 Gms. neostam.

Case 25: 36 year old, white, AAF; served only in England, France, and Germany; only residence in endemic area was in Nice on the Riviera from 17 to 24 June 1945. Sudden onset of fever, chill, and headache on 9 July 1945. Hospitalized same day with diagnosis of influenza. Original symptoms continued plus anorexia, diarrhea, and weight loss. Wide swings of temperature with double diurnal rises. Malaria, typhoid fever and undulant fever considered but not established by laboratory tests. On 26 July the RBC had fallen to 3.4 with 70% hemoglobin and WBC was only 6,250 with 66% neutrophils in the face of high fever. Spleen enlarged gradually to reach almost to the umbilicus on 14 August. L.D. bodies demonstrated in sternal marrow on 16 August, and were also found in an inguinal lymph node biopsy. Treated with 1.9 Gms. tartar emetic 17 August to 16 September inclusively. Developed bronchopneumonia for which he received 40,000 units of penicillin q. 3 hr. from 22 to 30 August inclusively. Temperature fell to normal on 31 August but rose again on 3 September when a diagnosis of lung abscess was made. This was treated with penicillin and sulfadiazene and the temperature fell to normal on 14 September remaining so thereafter. On arrival in the United States he was afebrile and was essentially asymptomatic and the blood count was normal. No attempt was made to find leishmania but he was given 2.6 Gms. neostibosan 15 to 25 October inclusively. On arrival in Moore General Hospital on 1 November he complained only of slight residual weakness and some numbness of the toes. Physical examination was essentially negative. Blood count and urinalysis normal, serum protein normal, sternal marrow normal, chest x-ray showed scarring in right upper lobe and adhesions at left base. Discharged to duty 15 March 1946.

Comment: Acute onset with fever, chill, and headache. L.D. bodies demonstrated in sternal marrow and lymph node 38 days after hospitalization. Treated with 1.9 Gms. tartar emetic. Treatment period complicated by pneumonia and lung abscess. Given 2.6 Gms. neostibosan one month after completion of tartar emetic without clinical or laboratory evidence of failure of previous treatment. Discharged to duty 6 months after completion of original treatment.

Case 26: 30 year old, white, AAF, India-Burma-China, October 1943 to September 1945. Onset about 1 May 1945 with chills, fever, sweats, dull headache and mild unproductive cough. Reported to sick call 7 May 1945; temperature 102.6, some enlargement of posterior cervical lymph nodes, few moist rales over left upper lobe posteriorly, liver edge just pal-

pable. Hospitalized 11 May; liver palpable and not tender, spleen down 2 finger breadths, smear negative for malaria, WBC 6,500 falling to 1,850 on 15 May, temperature rising to over 104° daily with double peaks, chest x-ray and agglutinations negative. Sternal marrow 18 May showed L.D. bodies. Treated with 3.8 Gms. neostam 19 to 30 May inclusively. Temperature became normal on 8th day of treatment. WBC rose to exceed 4,000 during treatment. Spleen just palpable at end of treatment. Subsequent course afebrile and asymptomatic. In Moore General Hospital 14 October 1945 to 7 February 1946. Physical examination, blood count, urinalysis and serum proteins normal.

Comment: Acute onset with chill, fever, sweats, headache and unproductive cough. Early leucopenia. L.D. bodies demonstrated in sternal marrow on 8th day of hospitalization. Successful treatment with 3.8 Gms. neostam.

Case 27: 26 year old, white, AAF, India. Native contacts, rope beds, thatched huts. Became acutely ill 3 August 1945 with anorexia, nausea, vomiting, and weakness. Developed chills, fever, and headache 14 August for which he was admitted to Station Hospital 17 August. Wide temperature swings at 104° and 105° daily. Initial WBC was 1,400 with 62% lymphocytes. RBC 4.8. Leishmaniasis suspected. Transferred to evacuation hospital 24 August. Spleen noted 5 cm. below costal margin on admission; WBC 3,000 with 51% lymphocytes; RBC 3.5, hemoglobin 70%. Icterus index 31, serum albumin 3.2, globulin 4.1 on 26 August. L.D. bodies and gametocytes of *P. vivax* found in sternal smear on 26 August. Spiking fever continued and weight fell 40 pounds before treatment. Given 2.6 Gms. neostibosan, followed by 2.7 Gms. neostam from 29 August to 16 September inclusively. A second sternal puncture on 6 September again showed L.D. bodies and *vivax* gametocytes. Though repeated blood smears failed to show malarial parasites, full dosage of atabrine was started on 6 September without effect on fever. Temperature fell to normal on 15th day of antimony treatment, and patient remained afebrile and essentially asymptomatic thereafter. During first week of treatment spleen enlarged to umbilicus and liver became palpable; during last half of treatment, spleen began to shrink and liver could no longer be felt. The icterus index fell to 20 on the second day of treatment and to 10 two weeks later. The first significant improvement in blood count was noted on 27 September—WBC 4,800, hemoglobin 97%. Evacuated to United States 16 October. Arrived at Moore General Hospital 29 November, essentially asymptomatic and having regained 20 pounds to reach 196. Weight 213 before discharge on 10 February 1946 at which time examination was negative except for barely palpable spleen. Blood count, urinalysis, serum protein, icterus index, bromsulfalein excretion normal on discharge; cephalin flocculation still weakly positive, thymol turbidity 3.7 units.

Comment: Acute onset with anorexia, nausea, vomiting and weakness followed in 10 days by chills, fever, and headache. Icterus clearing quickly. Marked early leucopenia. Diagnosis established by sternal puncture on 9th day of hospitalization. Treated with 2.6 Gms. neostibosan followed by 2.7 Gms. neostam. Uneventful convalescence. Leishmaniasis apparently became manifest during infectious hepatitis, the latter improving markedly before institution of treatment for leishmaniasis.

Case 28: 30 year old, colored, Quartermaster. North Africa and Sicily 15 months, 1943 to 1945. 6 weeks after landing in North Africa, hospitalized for an illness characterized by fever, headache and generalized urticaria, diagnosed as German measles. A month later readmitted for headaches and nervousness and from this time was never entirely up to par. Became acutely ill in September 1945 with fever, chilly sensation, anorexia, nausea, and some vomiting of approximately 3 weeks duration. During this time patient states that the urine became dark and that he developed nocturia (3 to 4 times nightly). Hos-

pitalized 7 October 1945. Palpable spleen. Temperature spiking to 103° or 104° daily r chills. Malaria smears, blood culture, agglutinations, and chest x-ray negative. W 4,200 on admission, falling to 2,450 a week later. Icterus index normal. Generali lymphadenopathy noted 22 October 1945 and axillary node was biopsied. Quinine, a brine, and penicillin given without effect on fever. Since the RBC had fallen to 2.8 or October two transfusions were given. Formol-gel positive 20 October; sternal punct on 13, 21, and 31 October and 22 November were all negative as was also the lymph n biopsy. Despite failure to establish etiological diagnosis he was given 2.55 Gms. neost between 30 November and 10 December with dramatic clinical improvement and was tl evacuated to United States. Patient states that he received further injections while route but no record of this is available. Admitted to Moore General Hospital 21 Janu 1946 complaining of fever, headache, nervousness and extreme weakness. Soft, non-ten spleen two finger breadths below costal margin. Generalized mild lymphadenopat Spiking temperature up to 104 with some double peaks. WBC 2,800, RBC 3.4, hemoglo 61%. Clotting 30 minutes (Lee-White) with no retraction at 2 hours but fairly good retr tion at 24 hours. Routine urinalysis showed specific gravity 1023, trace of albumin, 5 8 RBC, no casts. B.U.N. 14 mgm %, serum albumin 3.0, globulin 5.8, formol-gel positi Splenic puncture positive for L.D. bodies 29 January 1946. Treated with 5.0 Gms. neostil san between 30 January and 14 February 1946. No fever after 7th day of treatment. apparent toxicity; urine showed a little albumin and occasionally a few RBCs until February, but this is probably related to the disease rather than the medication si similar findings were recorded at Moore General Hospital before treatment and overs before any treatment. One month after completion of treatment, weight had risen pounds and spleen was distinctly smaller. On return from furlough 28 May white blo count and urinalysis were normal. Because of the urinary findings in this case, PSP a urea clearances were done before discharge and were normal. Serum proteins normal pr to discharge on 30 June 1946.

Comment: Acute onset with fever, chilly sensation, anorexia, nausea a some vomiting. Sternal puncture and lymph node biopsy were negative. Giv 2.55 Gms. neostam, nevertheless, with temporary improvement. Subseque recurrence of fever and symptoms. L.D. bodies demonstrated by splenic pun ture. Presumptive cure after 5.0 Gms. neostibosan. Microscopic hematu on numerous occasions prior to and during both treatment courses; none sin successful treatment.

Case 29: 24 year old, colored, Quartermaster Corps and Military policeman, India theat February 1944 until January 1946. Acute onset with fever without chill on 21 Septemb 1945. Had intermittent fever from then until 7 October 1945 when he was hospitalize Daily temperature rises continued to 103° to 105° without other symptoms until 12 Nove ber 1945 when temperature spontaneously subsided. However, fever recurred again with 10 days and then remained a constant feature until diagnosis and treatment. Spleen bare palpable. On 31 November 1945 diagnosis of leishmaniasis made by the demonstration parasites in bone marrow smears. Treatment, 3.5 Gms. neostibosan from 1 December 19 to 12 December 1945. Fever subsided within 9 days and there was marked clinical improv ment. On arrival in the United States the red blood count and white blood count we normal but the serum globulin was still 4.5 Gms.% and the cephalin flocculation strong positive. No relapse occurred during a period of 6 months observation. On discharge a laboratory and clinical studies were negative except that the cephalin flocculation test w still positive, and the serum globulin slightly elevated.

Comment: Typical onset with fever of a daily intermittent type. Sponta neous remission of temperature lasting about 10 days. Presumptive diagnos

in this case was malaria at first and then for several weeks typhoid fever. Kala-azar was established by bone marrow puncture. Good clinical response and apparent cure from a relatively small amount (3.5 Gms.) of neostibosan. Persistence of positive cephalin flocculation for 6 months.

Case 30: 26 year old, colored, Mechanic, India August 1944 to December 1944. Onset 10 October 1945 with malaise, anorexia, chills, fever, night sweats, severe occipital headaches, and weakness. Treated as ambulatory patient until 25 October. Then hospitalized for 19 days during which time no diagnosis was established but fever subsided. Rehospitalized 19 November, 6 days after discharge. Temperature ranged to 101 6°. WBC 3.5, RBC 4.3 on admission falling slightly subsequently. Repeated malaria smears, agglutinations, stool and urine examinations all normal. Transferred to another hospital 29 November. Liver and spleen enlarged. RBC 4.2, WBC 5,900. Serum albumin 3.5, globulin 4.5. L.D. bodies demonstrated by sternal puncture on 1 December 1945. Treated with 3.4 Gms. neostibosan, 2–13 December, fever subsiding before end of treatment. Evacuated to U.S. for convalescence. Arrived Moore General Hospital 30 January 1946. Afebrile. Spleen down 1 finger breadth. RBC 4.9, WBC 4,850. Serum albumin 4.6, globulin 4.0, formol-gel negative. Sent to furlough without treatment. On return, 22 March, still afebrile and asymptomatic and spleen just palpable. WBC 2,200. Leucopenia persisted and low grade fever recurred in April. Sternal punctures on 10 and 23 April negative. Treated on clinical grounds with 5.0 Gms. neostibosan, 25 April to 11 May. No fever after 1 May, 1946. Subsequent febrile episode presumably due to recurrent thrombophlebitis. Convalescence otherwise uneventful.

Comment: Acute febrile onset with brief spontaneous remission. Diagnosis by sternal puncture 36 days after hospitalization. Presumable treatment failure with 3.4 Gms. neostibosan. Presumptive cure after retreatment with 5.0 Gms. neostibosan.

REFERENCES

1. Price, F. L., and Myer, R. A.: Kala-azar (a case). J. A. M. A., **125**: 490, 1944.
2. Munter, E. J., and Packchanian, H. J.: Two Exogenous Cases of Visceral Leishmaniasis (Kala-azar) in the United States with Notes on Cultivation of Leishmania-Donovani in Vitro. American J. Trop. Med. **25**: 507 (Nov.) 1945.
3. Rose, H. M.: Cold Hemagglutinins in Visceral Leishmaniasis (Kala-azar). Proc. Soc. Exper. Biol. & Med. **58**: 93, 1945.
4. Mathieson, D. R., and Watson, B. A.: Kala-azar, A Case in the United States. J. A. M. A., **112**: 309, 1939.
5. (a) Kaminsky, F., Weven, G. K.: Visceral Leishmaniasis, N. Y. State J. M. March 1946.
   (b) Manple, C. D.: Visceral Leishmaniasis (Kala-azar) Report of a Case. In press.
   (c) Burchenal, J. H., and Woons, R. P.: Report of 3 cases of Visceral Leishmaniasis in members of Armed Forces of U.S. War Medicine **7**: 173 (March) 1945.
   (d) Leishmaniasis Among American Troops in the Mediterranean Theater of Operations. Kranes, A. Report of 5 cases submitted to S. G. O.
6. Hayman, J. H., Jr.: Personal Communication.
7. Lee, C. U., and Chuno, H. L.: A Clinical Study of the Early Manifestations of Chinese Kala-azar, Chinese Med. J. **49**: 1281 (December) 1935.
8. Angevine, D. M., Hamilton, T. R., Wallace, F. G., and Hazarp, J. B.: Lymph Nodes in Leishmaniasis, Am. J. Med. Sci. **210**: 33, July 1945.
9. Sweeney, J. S., Friedlander, R. D., and Queen, F. B.: Kala-azar (Visceral Leishmaniasis) Simulating Splenic Anemia, J. A. M. A., **128**: 1020, (4 August) 1945.

10. (a) Huang, C. H.: Acute Agranulocytosis in Kala-azar. Chinese Med. J. **57**: 119, February 1940.
(b) Zia, L. S. and Forkner, C. E.: The Syndrome of Acute Agranulocytosis and its Occurrence as a Complication of Kala-azar. Am. J. Med. Sci. **188**: 5, November 1934.
11. Walter Reed General Hospital.
12. Ling, S. L. Distribution of Protein Fractions in the Serum of Kala-azar Patients. Proc. Soc. Exp. Biol. **27**: 247, 1930.
13. Wertheimer, E., and Stein, L.: The Cold Susceptible Globulin Fraction of Pathologic Sera, J. Lab. Clin. Med. **29**: 1082, 1944.
14. Gutman, A. B., and Gutman, E. B.: Calcium Protein Relation in Hyperproteinemia: Total and Diffusible Serum Calcium in Lymphogranuloma Inquinale and Myeloma, Proc. Soc. Exp. Biol. **35**: 511, 1936.
15. Huei-Lan Chung: The Sedimentation Rate of the Blood of Patients with Kala-azar, Chinese Med. J. **48**: 11, November 1934.
16. Scovel, F. G.: Kala-azar: A Review of Its Incidence and Epidemiology in China and Clinical Observations on 585 Cases, Annals of Internal Medicine **21**: 607 (October) 1944.
17. Yang, C. S., Ch'en, K. T.: The Blood Platelets in Kala-azar, Nat. Med. J. of China, **16**: 34, 1930.
18. Rhoads, C. P., and Miller, D. K.: Histology of the Bone Marrow in Aplastic Anemia, Arch. of Path. **26**: 648, 1938.
19. History of Internal Medicine: India-Burma Theater, Blumgart, H. L., and Pike, G. M.
20. E. T. M. D. (a) North Africa, 1 May 1944.
(b) India-Burma, 9 February 1945.
(c) India-Burma, 13 February 1945.
(d) India-Burma, 1 July 1945.
21. Wise, C. R., and Gutman, A. B.: The Formol Gel Reaction: A Convenient Preliminary Test for Hyperglobulinemia. Am. J. Med. Sci. **194**: 263, 1937.
22. Knowles, R.: Cited by Strong, R. P.: Diagnosis Prevention and Treatment of Tropical Diseases. 7th Ed. 1944, The Blakiston Company, Philadelphia.
23. Henderson (1936), Wang (1938). Cited by Strong, R. P. Vol. 1, p. 277.
24. Strong, R. P.: Diagnosis, Prevention and Treatment of Tropical Diseases, Vol. 1, p. 256, 7th Ed., Philadelphia, The Blakiston Co.

INVOLVEMENT OF THE NERVOUS SYSTEM BY MALIGNANT LYMPHOMA

H. J. SPARLING, Jr., M.D., R. D. ADAMS, M.D. and F. PARKER, Jr., M.D.*

Involvement of the nervous system by malignant lymphoma constitutes an infrequent yet well recognized form of neurological disease. A literature of large proportions has accumulated on this subject and to add another contribution requires a preliminary word of explanation. Most of the published accounts consist of individual case reports by clinicians or pathologists who have had some personal encounter with this type of disease. In those instances where the pathological anatomy is well presented the clinical aspects are slighted, or the reverse is true. No attempt has been made to present to neurological physicians a well balanced conception of the different varieties of lymphomas as they affect the nervous system. The aim of the present communication is therefore to set on record the large body of clinical and pathological data which has been collected at the Mallory Institute of Pathology and to bring to the attention of neurologists a useful classification of these diseases based on histogenesis that has been adopted by this laboratory.

HISTOGENETIC CLASSIFICATION OF LYMPHOMAS

The classification that we have accepted is one which is based on the histology of the principal cell type of the tumor. This is the only practical classification which can be used since the etiology of these diseases is unknown and the gross pathology and clinical manifestations of the different types of lymphomas are not sufficiently distinctive. The validity of the histologic criteria of the different lymphomas has been well established in this laboratory over a period of years through the studies of Mallory, Parker and Jackson. The value of dividing the lymphomas in this way has been proven on innumerable occasions by the relative accuracy with which the clinical course of the disease can be predicted from an examination of a lymph node. It must be remembered, of course, that any pathological diagnosis based on the microscopic examination of a single lesion may at times fail to represent accurately the character and extent of the disease in other organs.

The terminology in this field is confusing and inexact. For example, lymphoblastoma has been applied to the entire group of these diseases by some writers and to a specific type of lymphoma by others. The terms reticulum cell sarcoma, clasmatocytoma, microglioma, have all been used to refer to the same type of tumor. Although a new terminology would be desirable this is probably impractical since many of these names have become firmly embedded in medical parlance by habit and custom. The most that can be expected, then, is that

* Mallory Institute of Pathology and Neurological Unit, Boston City Hospital and the Department of Neurology, Harvard Medical School.

each term be so well defined that all workers will understand what is meant by it.

In this article we follow the practice of many workers in using the generic term lymphoma to refer to all neoplastic diseases arising from the constituent cells of lymph nodes. The special cells of the lymph node are the mature lymphocyte, its progenitor the lymphoblast, the reticulum cell and the plasma cell. Since the connective tissue elements and blood vessels are common to all tissues these are not regarded as characteristic of the lymph node. Each of these specific cell types is capable of undergoing neoplastic transformation. The tumor reproduces more or less faithfully the cells from which it is derived. Since lymphoid elements are found in many tissues a lymphoma can originate in any organ and, once developed, may become diffuse either by the formation of multicentric foci or by hematogenous or lymphogenous metastases.

The derivation of the lymphomas and the transition of one form of lymphoma to another are shown in Table I.

In considering lymphomatous diseases of the nervous system only one modification of the above classification need be made. As yet there has not been a well authenticated recorded case of Hodgkin's paragranuloma or granuloma of the brain or spinal cord.

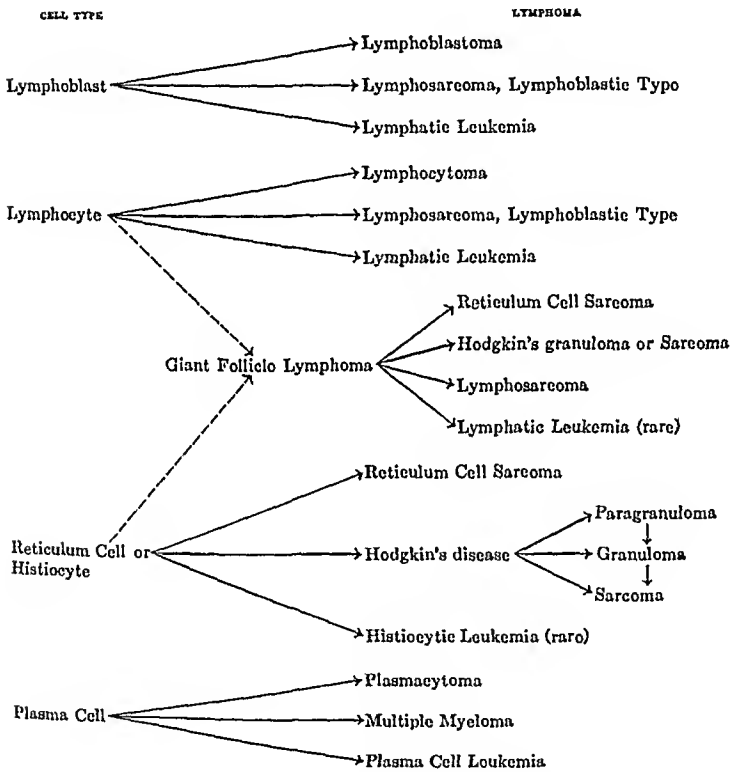
The histological characteristics of these tumors have been described in detail elsewhere, (1, 2, 3, 4). In order to better acquaint neurologists with the more recent refinements in the microscopic pathology of lymphomas the characteristic features of each type are summarized below.

1.-*Lymphocytoma, Lymphosarcoma, lymphocytic type and Lymphatic Leukemia.* The cell type of this tumor is the mature lymphocyte. These cells are small, ranging in size from 8 to 10 micra, have a round nucleus containing heavy masses of chromatin and a scant basophilic cytoplasm. They accumulate in large aggregations destroying the normal architecture of the node and infiltrating its capsule (See Fig. Ib). Mitoses are infrequent. There are no giant or multinucleated cells and the reticular connective tissue as demonstrated by silver stains is not increased in amount (cf. Fig. IIIc). Involved lymph nodes are enlarged, firm, and on cross section are homogeneous and pink. When the disease is confined to one or several lymph nodes or occurs as a non-invasive nodule of lymphoid tissue it is classified as lymphocytoma. When a mass of such cells, developing in some tissue containing lymph follicles, invades locally and does not metastasize widely lymphosarcoma of the lymphocytic type is the proper term. When in addition to either lymphocytoma or lymphosarcoma there is clinical evidence of large numbers of lymphocytes or lymphoblasts in the circulating blood and at autopsy widespread infiltration of liver, kidneys, spleen, bone marrow and other viscera is found, the disease should be designated as lymphocytoma or lymphosarcoma with lymphatic leukemia. Except for extent and distribution of the lesions, lymphocytoma, lymphosarcoma and lymphatic leukemia cannot be distinguished from one another microscopically.

2. *Lymphoblastoma, Lymphosarcoma, lymphoblastic type and Lymphatic Leukemia.* When the cell type of the tumor resembles the young lymphocyte or

lymphoblast, this attribute should be indicated by the term lymphoblastoma. These cells are larger than the mature lymphocyte, varying from 10–20 micra in size. The nucleus is larger, with a clearly defined nuclear border and evenly dispersed, finely divided chromatin. The cytoplasm is small in amount and appears as a narrow border which is basophilic in staining reaction (See Fig. Ia).

TABLE I



Mitotic figures are usually numerous. There are no multinucleated cells and the reticulum is not increased in amount. Areas of necrosis are seldom seen. The tumor cells destroy the architecture of the lymph node and may invade the capsule of the node.

Like lymphocytoma the term lymphoblastoma is restricted to involvement

of nodes and non-invasive nodules in lymphoid tissue. When lymphoblasts grow as an invasive tumor mass lymphosarcoma, lymphoblastic type is the appropriate designation (cf. Fig. Ic). If either lymphocytes or lymphoblasts circulate in the blood stream and infiltrate many organs without tissue destruction, the condition is called lymphatic leukemia. At autopsy widespread visceral involvement and splenomegaly are the rule. In adults, at least, the lymphoblastic form of the disease is less frequent than the lymphocytic type.

3. *Giant Follicle Lymphoma.* Histologically the giant follicle lymphoma is composed of numerous large lymphoid follicles often of such size as to be visible with a hand lens (see Fig. Id). The centers of these follicles are filled with actively proliferating young lymphocytes or reticulum cells. At the periphery of the follicles there is a narrow zone of closely packed mature lymphocytes Fusion of adjacent follicles may occur. Between the large follicles numerous adult lymphocytes are usually present. The reticulum is compressed by expanding follicles.

Although giant follicle lymphoma is usually limited to lymph nodes and spleen and rarely involves the other internal organs, it is noteworthy that in more than half the cases metamorphosis into Hodgkin's granuloma or sarcoma, lymphosarcoma or reticulum cell sarcoma occurs. In such cases the disease assumes the characteristics of the more malignant form of the disease.

4. *Hodgkin's Disease.* The common denominator of all forms of Hodgkin's disease is the Reed-Sternberg cell. If not present a histological diagnosis of Hodgkin's disease cannot be made. The typical Reed-Sternberg cells measure 10 to 40 micra in size and have abundant finely reticulated acidophilic or basophilic cytoplasm. The nucleus is pleomorphic and may be lobulated or multilobed. Multinucleated cells also occur. The nuclear chromatin is distributed in heavy clumps and large nucleoli are characteristically present.

The identification of the Reed-Sternberg cells is not always easy. They may be confused with tumor giant cells or megakaryocytes. Errors of this type can usually be avoided by taking account of the histology of the whole microscopic section.

a) Hodgkin's paragranuloma is the most benign form of the disease and its existence has been doubted by some pathologists. This point need not be argued here because, as stated above, there are no known cases of paragranuloma of the nervous system. The characteristic features are the partial or complete obliteration of the nodal architecture by a diffuse infiltrate of adult lymphocytes and the presence of few or many Reed-Sternberg cells, reticulum cells, and plasma cells. Eosinophils, although they may be present, are never numerous and necrosis and fibrosis do not occur. Most frequently a few cervical nodes are involved and these are discrete, of rubbery consistence, and yellowish-gray on cut section. Usually the disease is limited to the lymph nodes and does not involve the viscera unless transition to Hodgkin's granuloma has occurred. Rarely there is widespread involvement of the internal organs by lesions showing the histologic characteristics of Hodgkin's paragranuloma.

b) Hodgkin's granuloma is the most frequent form of this disease and is

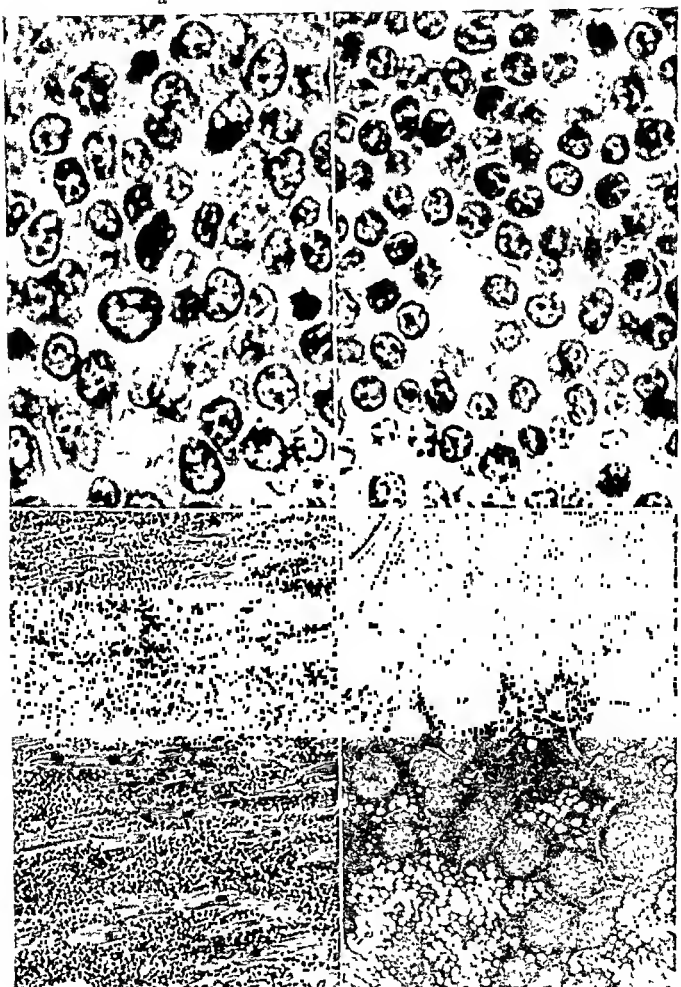


FIG. I. a. (Upper left.) Lymphoblastoma. Phloxine-methylene blue stain. ×660
b. (Upper right.) Lymphocytoma. ×660. c. (Lowe
left.) Lymphosarcoma invading the n lue stain. ×21
d. (Lower right.) Giant follicle lym... and eosin stain
×80.

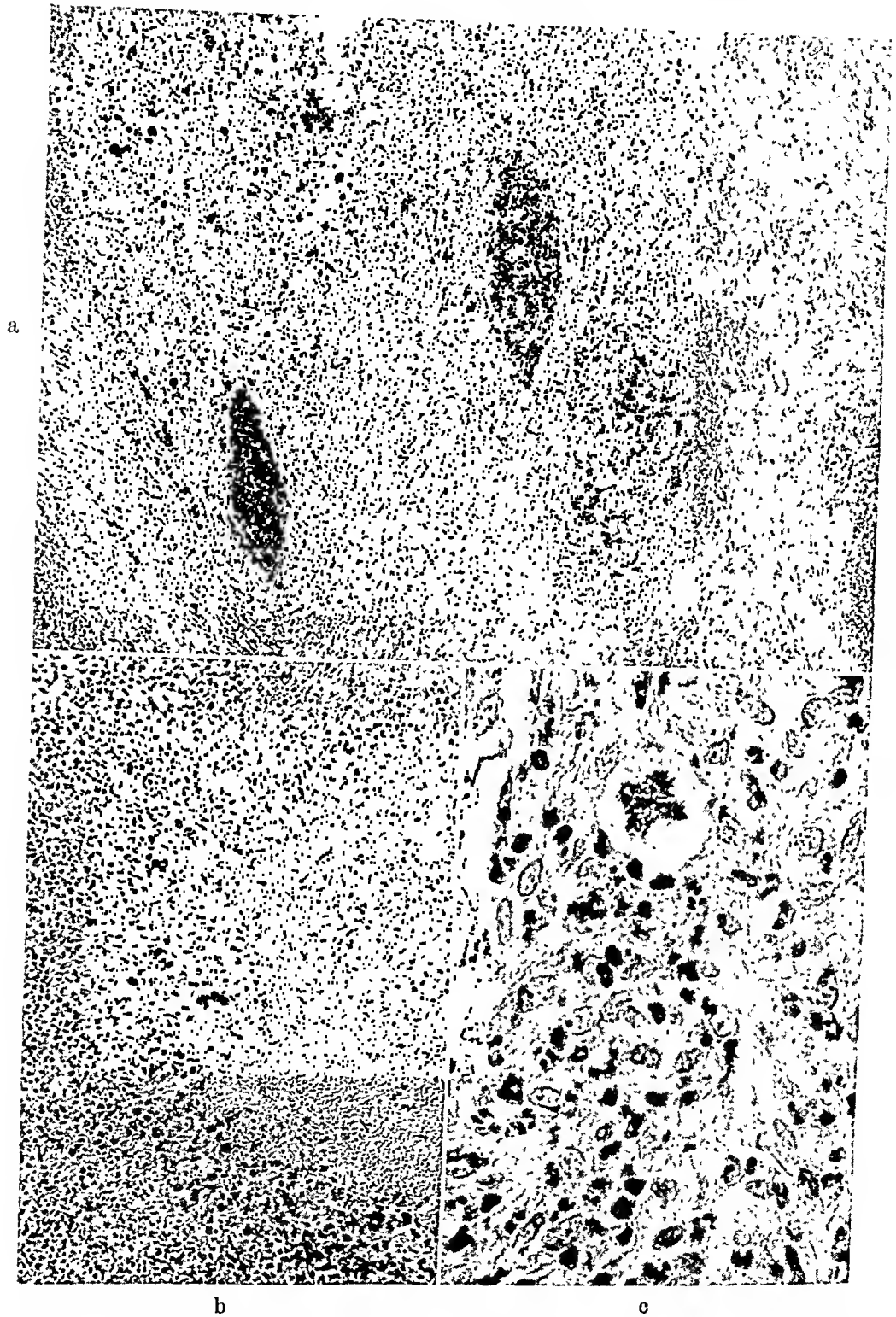


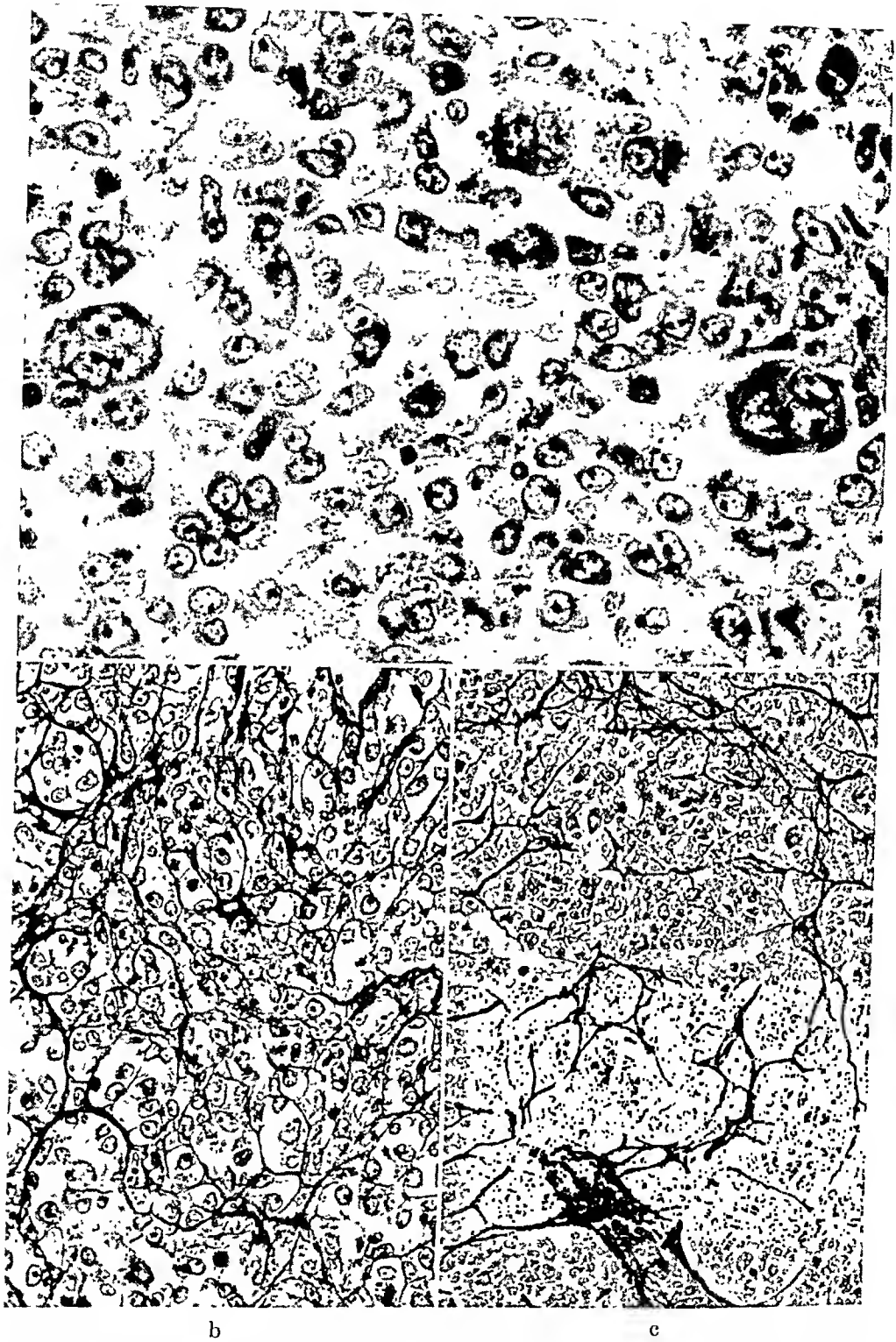
FIG. II. a. (Upper.) Hodgkin's granuloma showing broad bands of fibrosis. Note numerous giant cells. Phloxine-methylene blue stain. ×100. b. (Lower left.) Hodgkin's granuloma showing a large area of necrosis. Phloxine-methylene blue stain. ×200. c. (Lower right.) Hodgkin's granuloma showing eosinophilic polymorphonuclear leucocytes. Note giant cell in mitosis. Phloxine-methylene blue stain. ×400.

characteristically pleomorphic There are varying numbers of Reed-Sternberg cells, polymorphonuclear leucocytes, lymphocytes, plasma cells and reticulum cells Eosinophilic polymorphonuclear leucocytes are abundant in some cases and scarce in others Parts of the tumor frequently undergo necrosis and replacement fibrosis Neutrophilic polymorphonuclear leucocytes are usually present and are numerous when necrosis is extensive (See Fig IIa, b, c) The amount of reticulum is increased and fine argentophilic fibers separate groups of cells and encircle individual cells In the more fibrous parts of the lesion the intercellular fibers are collagenous Masses of these cells fill the sinusoids, replace the lymph follicles and invade the capsule and the surrounding tissue thus fusing several lymph nodes into a mass Although clinically the cervical lymph nodes appear to be the first involved, in most cases the retroperitoneal, mesenteric and mediastinal nodes are extensively implicated early in the course of the disease Occasionally only an isolated group of nodes is involved and rarely the disease is confined to a single organ with no lymph node involvement When Hodgkin's disease is widespread it may occur in the spleen, liver, bone marrow and lung and more rarely in the stomach, intestines, kidney, pancreas or any other organ containing lymphoid tissue Areas of fibrosis or necrosis may be visible grossly Occasionally Hodgkin's granuloma undergoes transition to Hodgkin's sarcoma and the clinical course progresses with greater rapidity

c) Hodgkin's sarcoma is a tumor composed of cells which resemble histiocytes both morphologically and physiologically These cells are quite large being of 2 to 3 times the diameter of a mature lymphocyte The nucleus is usually large, round or ovoid and has a prominent nucleolus The cytoplasm is abundant and is basophilic or neutrophilic Mitoses are numerous Varying numbers of Reed Sternberg cells are scattered through the tumor Lymphocytes and reticulum cells are present but neutrophiles, eosinophiles and plasma cells are rare unless necrosis has occurred In silver stains the reticulum fibers are increased in amount and enclose single cells and groups of cells (Fig III a, b, c) In gross appearance, extent and growth characteristics this tumor closely resembles Hodgkin's granuloma with the exception that the brain and gastro-intestinal tract are more frequently involved in Hodgkin's sarcoma and the spleen more often in Hodgkin's granuloma The cell of origin of Hodgkin's sarcoma is thought to be the reticulum cell, the histiocyte or their precursors

5 *Reticulum Cell Sarcoma* Reticulum cell sarcoma is a tumor made up of cells which range in size from 10 to 20 microns The nuclei are round or ovoid in shape and are often indented on one side When the tumor is well differentiated the nuclear chromatin tends to be finely divided and when undifferentiated it is more coarse and the nucleolus more prominent The cytoplasm of the cells is abundant and varies in its staining reaction Often there is evidence of ameboid activity as shown by irregular pseudopodal processes of the cytoplasm and nucleus (Fig IVa) Binuclear cells may be seen but not true tumor giant cells Tumor cells may invade veins in a rather characteristic way while leaving adjacent arteries undisturbed (Fig IVb) Silver stains demonstrate irregular

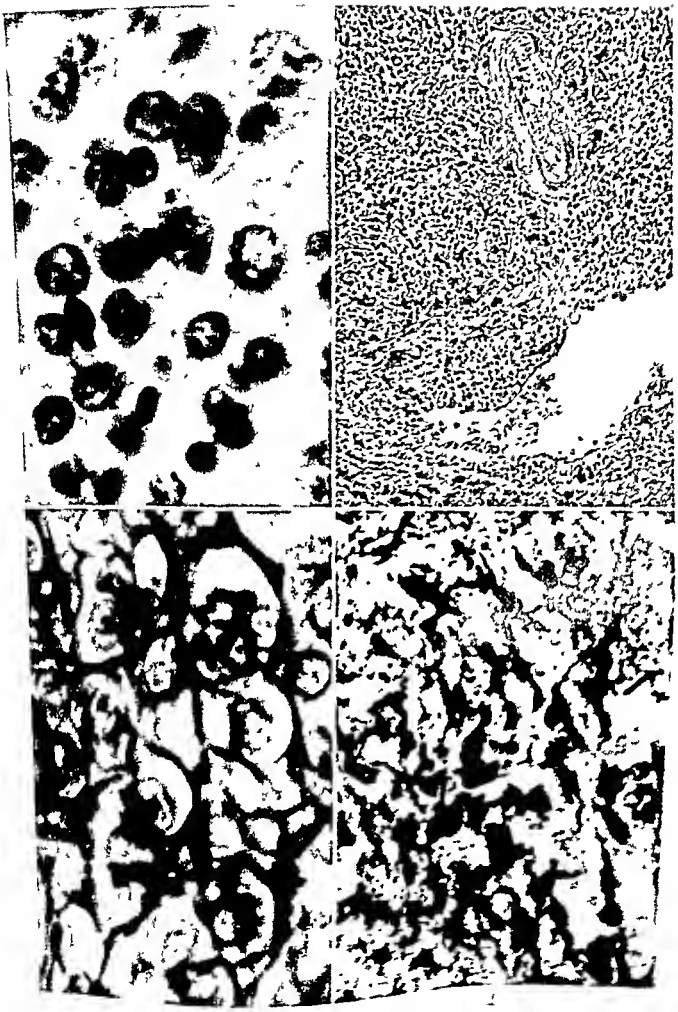
a



b c

FIG. III. a. (Upper.) (Case 9.) Primary Hodgkin's sarcoma of left frontal lobe showing typical Reed-Sternberg giant cells. Phloxine-methylene-blue. ×720. b. (Lower left.) Reticulum stain on tumor shown in (a). Fine reticulum fibers surround groups of cells and individual cells. Foot's reticulum stain. ×400. c. (Lower right.) Lymphosarcoma showing distribution of reticulum around blood vessels with only scattered fibers in tumor. Foot's reticulum stain. ×200.

a b



c d

FIG. IV a. (Upper left.) (Case 12.) Reticulum cell [illegible] tivity and [illegible] Pyronine methylene [illegible] lum cell [illegible] is not [illegible] Pyronine-methylene blue [illegible] Reticulum [illegible] individual tumor [illegible] stain. [illegible] b. (Lower right.) (Case 12. [illegible] are approx[illegible] brain. [illegible] carbonate [illegible]

fibrils of reticulum passing between groups of cells and surrounding individual cells, just like those in Hodgkin's sarcoma (Fig. IVc). Silver carbonate stains (Hortega) bring out the processes of the cells proving again their close kinship to the histiocyte, the reticulum cell and the microglial cell (Fig. IVd). The more anaplastic forms of this tumor are designated by some writers as stem cell sarcoma. Whether the tumor cells form the reticulum has not been decided.

In gross the tumor is firm and rubbery, grayish pink, homogenous or mottled. Many lymph nodes may be filled with tumor or solitary tumor masses may be confined to one organ such as a bone, spleen, heart, uterus or brain. Usually by the time death occurs there is multiple lymph node involvement. The common occurrence of the tumor in lymph nodes is the reason for including this tumor among the lymphomas even though, as would be expected, its derivation from histiocytes, reticulum cells or their progenitors permits it to arise in any organ.

6. *Plasmacytoma.* Although not universally accepted it is probable that multiple myeloma, plasmacytoma and plasma cell leukemia are all different manifestations of one disease. There is agreement on the fact that localized tumor masses of plasma cells may appear in lymphoid tissue in the absence of bone lesions or plasma cells in the circulating blood. Jackson, Parker and Bethea (4) conclude that "Multiple myeloma of the plasma cell type should be classed among the lymphomata. This type cell belongs beyond question to the lymphoid series and the clinical picture finds analogies throughout its course to the pathologic and symptomatic picture of lymphomata." It is in accordance with this view that involvement of the nervous system by tumors of the plasma cell type are considered here.

The cell type of this tumor is the plasma cell. These are somewhat larger than the mature lymphocyte with polygonal or somewhat triangular outline, a basophilic cytoplasm and an eccentrically placed, round nucleus containing heavy masses of chromatin often arranged at the periphery of the nucleus. Often numerous immature cells are present and binucleated and multinucleated cells may occur. Mitoses can usually be found (see Fig. Vb).

The tumor may remain localized in one organ for many years. In a case described by Jackson there was a plasmacytoma of the tonsil which spread to regional lymph nodes and 8 years later to bones. Usually at autopsy there are multiple bone lesions and occasionally extensive involvement of lymph nodes and viscera.

Leukemia

As mentioned above several varieties of leukemia are found in conjunction with lymphomas. In approximately one-third to one-half of the cases of lymphocytoma and lymphoblastoma lymphatic leukemia appears. Only a few cases of giant follicle lymphoma have been associated with abnormal lymphocytes in the peripheral blood. Leukemia is extremely rare in Hodgkin's disease although in a few cases of Hodgkin's sarcoma and of reticulum call sarcoma it has been observed and was of the histiocytic type. Occasionally plasma cell leukemia has been reported in cases of multiple myeloma.

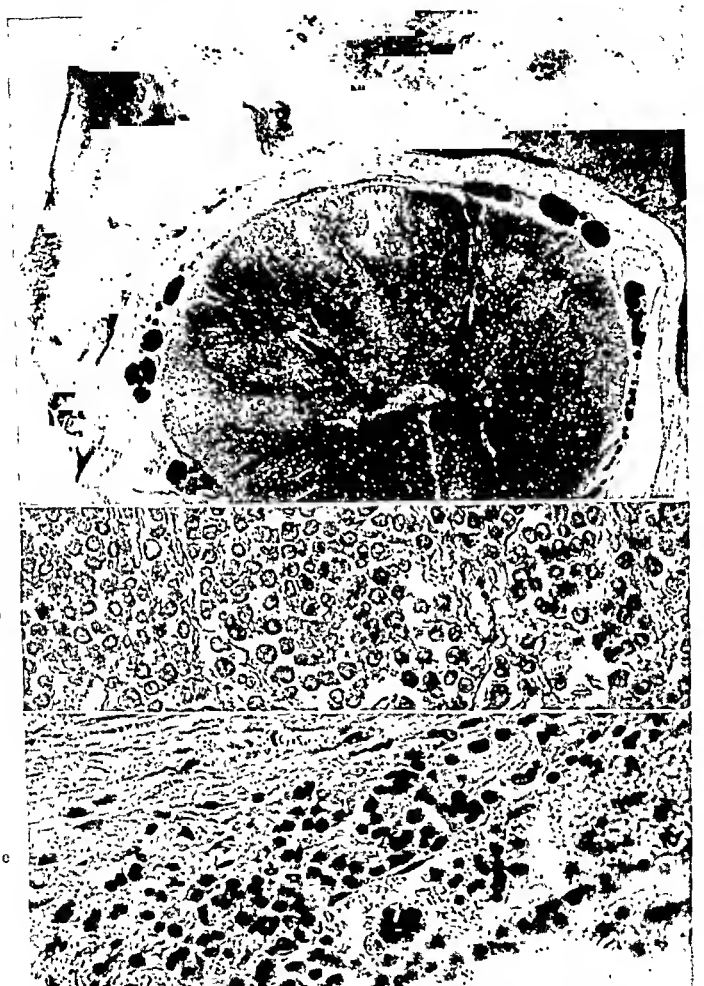


FIG. V. a. (Upper.) (Case 19.) Plasmacytoma of the spinal epidural space with secondary changes in the spinal cord due to compression. Cresyl violet stain. b. (Center.) (Case 19.) Plasmacytoma showing numerous immature plasma cells. Hematoxylin and eosin stain. ×400. c. (Lower.) (Case 19.) Plasma cells infiltrating the cranial dura. Hematoxylin and eosin stain. ×450.

Myeloid leukemia which is a neoplastic-like disease of the blood forming organs should not be classed under lymphomas because the myeloblast and myelocyte are not normal constituents of lymph nodes. Chloroma, so named because of the greenish appearance of the tumor masses, was formerly confused with malignant lymphomas. Here the tumor cells are also of the myeloid series giving a positive oxidase reaction. The older idea that the tumor cells were lymphoblasts has been disproved. Chloroma differs from myeloid leukemia only in being more invasive. The nature of the greenish color is unknown.

The relation between the different types of lymphomas has already been pointed out. Where multiple biopsies or biopsy and later autopsy are available the tumor persists in the original form in 75–80% of the cases. In time the remaining cases assumed a more malignant form. Giant follicle lymphoma may be transformed into lymphosarcoma, Hodgkin's granuloma or sarcoma or reticulum cell sarcoma; Hodgkin's paragranuloma becomes granuloma and granuloma may change to sarcoma. Hodgkin's sarcoma, reticulum cell sarcoma and plasmacytoma retain their original form.

The Pathological Material

This report summarizes the pathological findings in the nervous system of 118 autopsied cases of malignant lymphoma. These cases were drawn from the files of the Mallory Institute of Pathology of the Boston City Hospital between the years 1930 and 1945 inclusive. During this period approximately 11,500 autopsies were performed. The brain and spinal cord were examined in only 52 of the 118 cases, but these included most of those in which neurological symptoms had occurred. Six additional cases in which only a surgical biopsy from the spinal epidural space was obtained are included because they illustrate important clinical syndromes. These include one case each of lymphosarcoma, Hodgkin's granuloma and reticulum cell sarcoma and three cases of plasmacytoma. Also, two other cases from another hospital, one of reticulum cell sarcoma and one of giant follicle lymphoma, are presented because they exemplify important pathological principles.

In the following table the frequency of nervous lesions in the different types of lymphoma, as determined by our autopsy material, is seen.

LYMPHOSARCOMA OF THE CRANIAL BONES, VERTEBRAE AND DURA MATER

To review the medical literature on this subject is difficult because of the aforementioned lack of uniformity in nomenclature. Many of the older published cases are not lymphosarcomas but are, instead, Hodgkin's disease or some other lymphomatous tumor. Often the pathological data are not presented in sufficient detail to permit accurate classification.

Virchow (5) as early as 1863 recognized lymphosarcoma as a separate type of tumor but Murchison (6) in 1870 was the first to describe a case in which a "lymphoblastoma" had invaded the dura near the foramen magnum. Mosler (7) in 1872 reported a case of lymphosarcoma in which the dura and the optic nerves were implicated and Roncelli (8) another in which the base of the skull

and the neighboring dura were infiltrated. According to Abbott and Adson and others who scrutinized these papers, the cases of Murchison and Roucelli were probably examples of Hodgkin's disease.

The first example of spinal lymphosarcoma was recorded by Guillain, Alajouanine and Perisson (9) in 1925. In this case the tumor was in the spinal epidural space and compressed the spinal cord.

In recent years several important studies of large series of lymphosarcomas have appeared. Davison and Michaels (10) in summarizing 27 cases, proved by biopsy or necropsy, found that 7 had neurological symptoms. Of the 4 autopsied cases, 3 had spinal epidural tumors with cord compression and 1 had metastatic lesions in the cranial dura. Of the 3 biopsied cases there was one in which the meninges of the posterior fossa were invaded, 1 with lung and thoracic

TABLE II

*Frequency of nervous system involvement in 118 cases of malignant lymphoma**

TUMOR	NO. OF AUTOPSIES	BRAIN INVOLVEMENT	SPINAL CORD INVOLVEMENT
Lymphosarcoma	9	0	0
Lymphocytoma with Lymphatic Leukemia	33	3	0
Giant Follicle Lymphoma	1	0	0
Hodgkin's Disease			
Paragranuloma	2	0	0
Granuloma	*21*	*0*	*0*
Sarcoma	19	3	2
Reticulum Cell Sarcoma	18	4	2
Plasmacytoma—Multiple Myeloma	15	3	2
	118	13	6

* Brains and spinal cords were examined in none of the 9 cases of lymphosarcoma, in 14 of the 33 cases of lymphocytoma, in 12 of the 21 cases of Hodgkin's granuloma, in 9 of the 19 cases of Hodgkin's sarcoma, in 7 of the 18 cases of reticulum cell sarcoma and in 10 of the 15 cases of multiple myeloma. In only 2 of the cases in which neurological symptoms were present was the nervous system not examined.

vertebral lesions and nerve root compression and 1 with extensive involvement of the face and a facial nerve palsy.

Other publications of note are those of Woltman (11) who in a study of nasopharyngeal tumors with neurological symptoms discovered several which had invaded the cranial bones and dura at the base of the skull; Baker (12) who reported 2 cases of spinal epidural lymphoma, one of lymphosarcoma and the other of "lymphoblastoma" and who emphasized the frequency of this tumor by stating that it represented 4 per cent of the surgically treated spinal cord tumors at the Mayo Clinic; and Verda (13) who observed that 15 to 25 per cent of cases of lymphosarcoma exhibit neurological symptoms at some stage of the illness and that 10 to 15 per cent have an epidural tumor mass at necropsy. Verda also discussed the different pathways by which lymphoma can reach the spinal epidural space.

From the papers mentioned in the foregoing paragraphs the frequency of lymphosarcomatous involvement of the skull, vertebrae, epidural space and meninges is emphasized. In many cases this occurred only after the disease had become generalized though in several the nervous lesion was the primary or first event in the illness. Abbott and Adson (14) in 1943 presented the clinical and pathological findings in 2 cases, 1 autopsied and 1 biopsied, of "Primary Intracranial Lymphosarcoma". The symptoms were headache, swelling and tenderness of the skull, dizziness, Jacksonian seizures, mental confusion and diplopia. These tumors invaded the skull bones and the dura as well as the pia-arachnoid. Through the courtesy of Dr. J. W. Kernohan we have examined these sections and have made reticulum stains of them. The biopsied case was lymphosarcoma whereas the autopsied case satisfied our criteria of reticulum cell sarcoma.

The general pathology and symptomatology of lymphosarcoma are well known and will not be discussed in this paper.

In our pathological material there were no cases of primary lymphosarcoma of the cranial bones or of the brain. We had only one case of lymphosarcoma of the spinal epidural space with spinal cord compression and unfortunately this one did not come to autopsy. It is our impression that this type of malignant lymphoma affects the nervous system less often than does Hodgkin's disease, reticulum cell sarcoma and plasmacytoma. Furthermore, judging from the literature, in most of the authentic cases the tumor arose in the mediastinal and retroperitoneal lymph nodes and extended through the intervertebral foramens or it grew into the vertebral body and then invaded the spinal epidural space. The spinal dura was usually not penetrated by the tumor and the neurological symptoms were the result of compression of the spinal cord and nerve roots. In a smaller number of cases extension to the base of the skull with invasion of the dura and cranial nerves occurred. The brain was compressed and at times tumor tissue extended through the leptomeninges. Focal or diffuse infiltration of the leptomeninges may develop, especially in the presence of lymphatic leukemia.

In the following case there was secondary involvement of the spinal epidural space by a lymphosarcoma.

Case 1. (S40–816) Female, age 62 years: The patient had an attack of "gastroenteritis" 6 weeks before entry which was followed by severe pains in the groin and anterior surfaces of both thighs. Two weeks later her legs became weak and, after a few days, the legs as well as the bladder and rectal sphincters were paralyzed. At the time of entry to the hospital there was a flaccid paralysis of both legs with absent abdominal diminished, patellar and Achilles reflexes and extensor plantar reflexes bilaterally. All forms of sensation were greatly impaired or absent below 10th thoracic segment. There was percussion tenderness over the 8th and 9th thoracic spines. The lymph nodes and the spleen were not palpably enlarged.

There was a trace of albumin in the urine and the sediment contained many clumps of white cells. The hemoglobin was 80 per cent and the white cell count was 7200 per cubic mm. with a normal differential count. The cerebrospinal fluid was yellow; there was a complete dynamic block; the protein was 680 mg. per 100 cc. and no cells were present. In x-rays of the thoracic spine there was destruction of the 7th and 8th thoracic vertebras.

A thoracic laminectomy was performed. A purplish tumor mass was found in the epidural space extending from the 6th to the 12th thoracic vertebras and was partly removed. During the ensuing 2 months there was no definite change in the neurological findings except for the appearance of "mass reflexes". A protracted course of x-ray treatment effected no change in the spinal symptoms. She was transferred to a nursing home, and her subsequent course is unknown to us.

Diagnosis: Lymphosarcoma involving the thoracic spine and epidural space and compression of the spinal cord.

Comment: The symptoms were those of subacute spinal cord compression. The painful nature of the illness, the rapidity of progression, the tenderness over spine and the x-ray findngs all attested the presence of vertebral involvement and to the epidural location of the lesion. Apparently the compression of the spinal cord caused irreparable damage because there was no improvement after operation or Roentgen therapy. The tumor was composed of lymphoblasts. There was some condensed connective tissue around the blood vessels but no reticulum between tumor cells. Although there was no clinical evidence of tumor elsewhere, one is not justified in concluding, without autopsy verification, that other organs were not involved.

BRAIN AND SPINAL CORD LESIONS IN LYMPHATIC LEUKEMIA

Disease of the peripheral and central nervous system in lymphatic leukemia has been the subject of numerous articles the most thorough of which are those of Trommer and Wohlwill (15), Diamond (16) Schwab and Weiss (17) and Leidler and Russell (18). All have emphasized the great frequency of brain lesions in all types of leukemia both acute and chronic.

In an analysis of 146 cases of leukemia with pathological changes in the brain and spinal cord which had been reported in the medical literature up to 1935 Schwab and Weiss found one or several hemorrhages in 32.2 per cent of the cases, infiltration of the leptomeninges in 17.8 per cent and of the cranial nerves in 15.8 per cent, accumulations of leukemic cells in the perivascular spaces or brain parenchyma in 15.7 per cent and spinal epidural tumors in 8.2 per cent. Leidler and Russell observed similar lesions in 80 per cent of their 67 autopsied cases. Diamond found some abnormality in the brains of 14 successive cases of leukemia though in several cases the changes consisted solely of acute alterations of the nerve cells. In all the reviews of this subject the incidence and character of the pathologic change was about the same for lymphatic as for myeloid leukemia. Since our topic is that of lymphoma of the nervous system myeloid leukemia will not be discussed.

We have examined the brain and spinal cord in 14 cases of lymphatic leukemia. From this material we have been able to verify many of the previously described neuropathological findings.

Leukemia infiltrations were present in 3 of these cases. In 2 of them the meninges were diffusely infiltrated and in the third there was a nodule of leukemic cells in the choroid plexus. (Fig. VIb and c) The most frequent gross lesion was one or several brain hemorrhages (5 out of 14 cases). Most often these were small and in the substance of the brain but in one case were in the subarachnoid space and dura. In the latter place they formed multiple ecchymoses rather than a large subdural hematoma. Unlike the spontaneous brain hemorrhages caused by hypertension and arteriosclerosis which are usually situated in the basal

ganglia the leukemic hemorrhage may occur in any of the brain. In one case the hemorrhage was large and probably was the cause of death; in the other 4 cases they were small and probably incidental. In or near these hemorrhages aggregates of leukemic cells could be seen microscopically. In most of the cases there were no gross abnormalities and on microscopic examination the only finding of note was the presence of large numbers of white blood cells in the capillaries and veins. In the perivascular space and in the meninges near these congested vessels there were often a few small collections of lymphocytes and lymphoblasts. In many instances one could not be sure whether this extravasation occurred during life or postmortem in the preparation of the section. Nerve cell changes consisting of faint or dark staining or shrinkage were observed frequently but were probably related to terminal events of the illness.

The clinical syndromes produced by these lesions are quite well described in the medical literature. Since neurological symptoms develop in approximately 20 per cent of cases of lymphatic leukemia, the greater frequency of the neuropathological changes would indicate that many of the lesions are agonal or occur in very sick patients who cannot be subjected to a complete examination.

Any patient with leukemia is very liable to apoplexy. This is usually manifested by the sudden onset of headache and confusion which progresses to coma, or by a sudden loss of consciousness. Hemiplegia, hemianesthesia, homonymous hemianopia or aphasia may develop. The cerebrospinal fluid may be clear or sanguineous and under increased pressure. The brain hemorrhage is usually attributed to thrombocytopenia though why it should occur in one part of one organ is not clear. Damage to a vessel by leukemic infiltration of its wall is said by some writers to account for the hemorrhage. The following case is illustrative of apoplexy in lymphatic leukemia.

Case 2. (A-41-309) Male, 14 years old: The patient had complained of weakness for about a month. Shortly before admission to the hospital numerous petechial hemorrhages were noted in the skin and he had a rather severe epistaxis.

The patient appeared chronically ill. Moderate pallor of the mucous membranes and numerous small hemorrhages in the skin of the extremities were present. All superficial lymph nodes were enlarged and the spleen was palpable 5 cm. below the costal margin. At this time he was alert and oriented and no neurological abnormalities were detected.

The hemoglobin was 35 per cent and red-cell count was 2,200,000. The white-cell count was 38,000 and the smear showed that 82 per cent of the cells were of the lymphocytic series, with many blast forms. The platelets appeared diminished.

On the evening of the 4th hospital day the patient complained of a severe headache and vomited. He was not observed carefully during the night and on the following morning was found comatose with a left hemiplegia. A lumbar puncture revealed grossly bloody cerebrospinal fluid under a pressure of 550 mm. of water. He died at noon about 18 hours after the onset of the headache.

Anatomical Diagnosis: Acute lymphatic leukemia and spontaneous hemorrhage in the right cerebral hemisphere.

Comment: Beneath the dura overlying both cerebral hemispheres there were many ecchymoses. The hemorrhages were not more than 1 mm. thick at any point. The brain was swollen and the convolutions were flattened. The right cerebral hemisphere in its midportion was 3.0 cm. wider than the left. Dark clotted blood filled the cisterna magna and some

issued from the fourth ventricle. On coronal section a large purplish-red blood clot 5.0 by 5.5 by 6.2 cm. was found in the white matter of the left frontal and parietal lobes and in the lenticular nucleus and internal capsule. It had ruptured into the body of the left lateral ventricle and the entire ventricular system was filled with blood. There were several small hemorrhages in the base and tegmentum of both the midbrain and pons. In microscopic sections there were no leukemic infiltrations of the brain or meninges.

One of the less frequent but more interesting neuropathological findings is leukemic infiltration of the leptomeninges sometimes with involvement of one or several cranial nerves. Grossly the arachnoid is grayish-white, thickened and opaque and scattered small grayish foci can be seen. In microscopic sections large masses of lymphocytes and lymphoblasts invade the pia and arachnoid and the perineurium of cranial nerves. Rarely a grossly perceptible mass of lymphoid cells is found in the brain.

Clinically these patients with infiltration of the meninges show symptoms of meningeal irritation or multiple cranial nerve palsies. Unilateral facial palsy or facial diplegia has been reported several times, and next in frequency is ocular palsy due to involvement of oculomotor, trochlear or abducens nerves. The neurological symptoms may fluctuate and respond temporarily to quite small, even diagnostic doses of x-ray. The cerebrospinal fluid is under normal or increased pressure and may contain as many as several thousand lymphocytes per cubic mm. Owing to the presence of glycolytic enzymes in leukemic cells the sugar content may in rare instances be quite low suggesting a bacterial meningitis. A striking example of lymphatic leukemia masquerading as a neurological disease was that reported by Schwab and Weiss (17). Since it is included in our pathological material we have summarized it below.

Case 3. (A-34-131) Male, 24 years old: The patient entered the hospital because of facial paralysis and difficulty in swallowing. The former symptom developed 8 days and the latter one 2 days before admission to the hospital. He also noted loss of taste on the left side of the tongue. In the past there had been no serious illness.

The patient was alert and rational. There was a paralysis of all the facial muscles on the left, a left palatal paralysis and absence of the left gag reflex. The remainder of the neurological examination was within normal limits. The lymph nodes and spleen were not enlarged. The white cell count was 14,000 with 40 per cent small lymphocytes as the only abnormality of the blood smear. The red cell count was 5,000,000.

On the 4th hospital day his temperature rose to 101 and white blood count was 19,000 with the same differential count. A diagnosis of bulbar poliomyelitis was considered. The cerebrospinal fluid pressure was 150 mm.; it contained 1900 lymphocytes per cubic mm. and a protein of 170 mg. per 100 cc.; the sugar and chloride values were normal and the Wassermann reaction was negative. On the 5th hospital day he developed a right facial paralysis. The neurological symptoms gradually receded but during the following month he developed an anemia, generalized lymphadenopathy and splenomegaly, and a peripheral blood picture consistent with acute lymphatic leukemia. The pleocytosis in cerebrospinal fluid varied from 400 to 4500 cells with an elevated protein and on one occasion the sugar level was 42 mg. There was a steady decline in his physical condition and he died on the 66th day in the hospital.

Anatomical Diagnosis: Lymphatic leukemia with infiltration of the leptomeninges, the right and left facial and the left glossopharyngeal nerves.

Comment: The facial and glossopharyngeal nerves were surrounded and infiltrated by

masses of lymphocytes and lymphoblasts. Similar cells were present in the pia and arachnoid (Fig. VI a and c) thus accounting for the pleocytosis in the spinal fluid.

Herpes zoster is a not infrequent complication of lymphatic leukemia or of other lymphomatous diseases and may at times call attention to the malignant tumor. The following case is illustrative.

Case 4. (A-45-527) Male, 56 years old: The patient was known to have chronic lymphatic leukemia. One week before entry he developed a band of vesicular lesions across the upper left quadrant of the abdomen. These vesicles were grouped together and each had an erythematous base. Within a day the eruption became generalized affecting even the mucous membranes. A biopsy was made of a skin lesion and was consistent with varicella or herpes zoster.

At the time of entry to the hospital the patient was quite emaciated and complained of pains all over his body and of weakness of his extremities. The tendon reflexes in the arms and legs could not be obtained. There were no objective sensory changes. His neck was slightly stiff. All superficial lymph nodes were enlarged, firm and non-tender; the spleen and liver were greatly enlarged.

The hemoglobin was 85 per cent, the red-cell count was 5,100,000 and the white cell count 10,600 with 70 per cent lymphocytes. The cerebrospinal fluid was under normal pressure, was xanthochronic and contained 2400 lymphocytes per cubic mm. and a protein of 160 mg.

The patient became confused and disoriented. There were gross twitchings of skeletal muscles. He had several generalized convulsions on the 7th hospital day and died.

Anatomical Diagnosis: Chronic lymphatic leukemia with leukemic infiltrations of liver, spleen, heart, kidney, leptomeninges and spinal ganglia; herpes zoster, generalized, with ganglionitis and meningitis.

Comment: In this case the infiltrations of the spinal ganglia and meninges consisted of lymphocytes, plasma cells and mononuclear cells (Fig. VI d). The heterogeneous character of these infiltrates was more suggestive of zoster than of leukemia. The necrotizing ganglionitis which we have observed in other cases of zoster was not present.

The pathogenesis of the meningeal, cranial nerve and brain infiltrations in lymphatic leukemia is not well understood. Apparently they may occur at a time when the peripheral blood is normal. Some pathologists regard such infiltrates as a transformation of existing mesenchymatous elements into leukemic cells rather than as metastases from a distant focus.

We have chosen to discuss spinal cord compression by leukemic tissue in the epidural space in the section devoted to lymphosarcoma. Infiltration of isolated peripheral nerves or of a plexus by leukemic cells or damage of such structures by hemorrhage is a rare neurological complication which was not observed in our material.

GIANT FOLLICLE LYMPHOMA IN THE SPINAL EPIDURAL SPACE

Reports concerning giant follicle lymphoma have in recent years established this lesion as a specific entity of potential malignancy. Brill, Baehr and Rosenthal (19), in the original description of the condition, designated this tumor as "giant follicular hyperplasia" but later classified it with the malignant lymphomas. Other names which have been assigned to it are follicular lymphoblastoma, giant follicle lymphadenopathy and malignant lymph follicle hyperplasia.

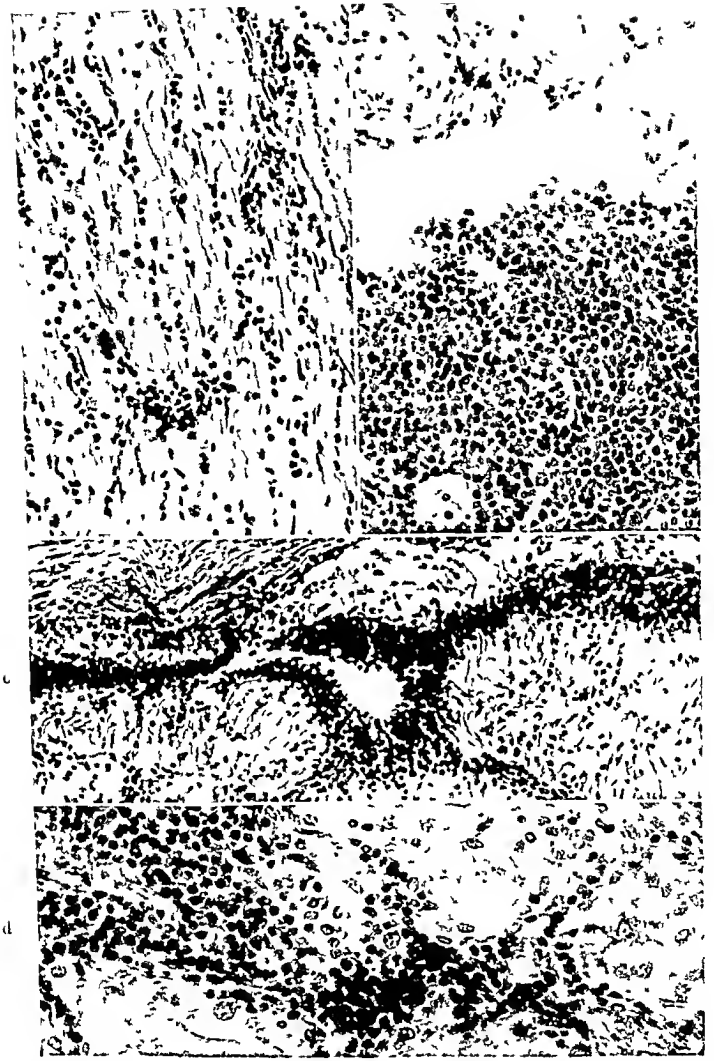


FIG VI a (Upper left) (Case 3) Lymphocytes infiltrating a cranial nerve in lymphatic leukemia Phloxine methylene blue ×400 b (Upper right) Nodule composed of lymphocytes in choroid plexus Case of lymphatic leukemia Hematoxylin and eosin stain ×400 c (Center) (Case 3) Infiltration of the dura by lymphocytes in lymphatic leukemia Hematoxylin and eosin stain ×150 d (Lower) (Case 4) Infiltration of a spinal root ganglion in lymphatic leukemia with herpes zoster Phloxine methylene blue stain ×100

The onset of the disease is insidious usually beginning with painless enlargement of regional lymph nodes or with generalized lymphadenopathy and splenomegaly. There is neither anemia nor abnormality of white cells in the circulating blood. Involvement of other organs such as the tonsil, liver, bone marrow, breast and gastrointestinal tract is infrequently found in later stages. The early lesions are quite radio-sensitive. Grossly the lymph nodes are firm and rubbery. On cut surface they are a pink or whitish color. The enlarged lymph follicles can be seen with a hand lens.

As pointed out by numerous authors (2, 20, 21, 22) the early course of the disease is benign but sometimes after a period of years have elapsed, there may be a change in the histology of the tumor to one of the more malignant types of lymphoma. A number of biopsy specimens have shown this transition in progress. It is estimated that 60 per cent of these cases terminate as Hodgkin's disease, reticulum cell sarcoma or lymphosarcoma.

Involvement of the nervous system by giant follicle lymphoma is extremely rare. To the best of our knowledge the only recorded instance of this complication is the case of Browder and de Veer (22). Their patient was a 39 year old woman whose initial complaint was pain in the thoracic spine which radiated anteriorly to the thorax. After 4 months there was progressive weakness and sensory impairment in the legs and lower trunk and sphincter incontinence. Laminectomy exposed a spinal epidural tumor which histologically was said to be a typical giant follicle lymphoma. Among the 25 biopsied cases reviewed by Jackson and Parker (2) there were none with lesions of the nervous system.

Only one autopsied case of giant follicle lymphoma is included in our material and this one did not affect the nervous system. However, Drs. T. Mallory and Charles S. Kubik (23) have made available to us a case which illustrates well the potentialities of this lesion once it assumes a more malignant form.

Case 5. (Mass. General Hospital—Autopsy 12017 Cabot case 32281) Female, 59 years old: The patient entered the hospital because of weakness and pain in both arms. Eighteen months before admission she developed a pain in the left thigh and weakness of the legs which gradually became worse. After seven months she could no longer climb stairs. Shortly afterwards she had sharp pains in her calves, hips, back and arms and an intermittent fever of 102° F. She also had tremors and weakness of both arms. During the past year she had lost 25 pounds in weight.

At the time of examination she appeared ill and was having considerable pain. The left pupil was larger than the right but both reacted normally. There was a firm, round, non-tender 3-cm. lymph node in the left axilla. At the right base the percussion note was dull and breath sounds were absent. The liver edge was palpated 5 cm. below the costal margin. The deltoid and biceps muscles on both sides were wasted and the biceps and radial reflexes were absent. There was also atrophy of quadriceps muscles and loss of knee and ankle jerks. The only demonstrable sensory changes were anesthesia of the left side of the chin and lower lip.

The red cell count was 4,200,000 and hemoglobin was 10.5 gms.; the white cell count was 7,300 with a normal differential. The serum phosphorus was 4.3 mg. per 100 cc. and the alkaline phosphatase 5.3 Bodansky units. The non-protein nitrogen was 24 mg. and the total protein was 7.0 gms. The spinal fluid protein was 125 mg. per 100 cc.

Supportive therapy was given but the patient became dyspneic and weak and died on the 10th hospital day.

Anatomical Diagnosis: Malignant lymphoma (giant follicle lymphoma and reticulum cell sarcoma) involving the retroperitoneal tissues and spinal meninges.

Comment: The neurological symptoms in this case consisted solely of pains, weakness and atrophy of the muscles of shoulder girdles and thighs and anesthesia over the left side of the chin. All of these symptoms and the loss of tendon reflexes pointed to involvement of multiple peripheral nerves or roots. The suspicion of lymphoma was confirmed by the biopsy of the enlarged axillary lymph node. At first the lymph node had the appearance of simple hyperplasia but on re-examination the lesion proved to be giant follicle lymphoma. The spinal cord appeared grossly normal at post-mortem examination but on more careful examination of the meninges several small tumor implants were seen. This process was most marked in the cauda equina and cervical cord segments. It was not sufficiently diffuse to account for the severe pains in all parts of the body unless nerves or roots were involved at some point other than the meninges. There was also extensive retroperitoneal lymphoma but here and in the meninges there was no trace of follicle formation. The tumor in its late phase had changed to a reticulum cell sarcoma.

HODGKIN'S GRANULOMA OF BRAIN AND SPINAL CORD

Hodgkin's granuloma is the most common and one of the easily recognizable forms of the lymphomas. It has been called lymphogranuloma and lymphadenoma but the eponymic terminology is still the most widely accepted.

Since the time of Murchison's (6) early report of central nervous system involvement by Hodgkin's disease many case records illustrating this form of the disease have been published. Ginsberg (24) in 1927 in a paper concerned solely with the neurological aspects of Hodgkin's disease described 10 cases and summarized previous writings on this subject. Not all of his cases were verified by autopsy but the majority were probably examples of Hodgkin's granuloma. In most of the cases there was tumor of the spinal epidural space which caused spinal cord compression. His fourth case was unusual in that there was involvement of the base of the skull and an epidural tumor in the posterior fossa but since both Hodgkin's disease and lymphosarcoma were said to have been present, the diagnosis appears uncertain. In one of the cases a clinical diagnosis of Hodgkin's disease of the left frontal lobe was made but was not confirmed pathologically.

Eugenis (25) was able to compile from the medical literature up to 1929, 54 cases of Hodgkin's disease involving the central nervous system. There were 12 cases with intracranial lesions and 42 with intraspinal lesions. Weil (26) in 1931 again reviewed the literature and summarized the clinical and pathological findings of 46 cases including three of his own. Viets and Hunter (27) in 1932 described seven cases of "lymphoblastomatous" involvement of the brain. Undoubtedly some of their cases were examples of Hodgkin's disease but the pathology as presented does not permit classification according to our terminology. Martin and Courville (28), Von Hagen (29), Gray, Baker, Cotrell and Kogland (30), Winkleman and Moore (31), Verde (13) and Jackson and Parker (32) have also contributed important papers. The last named writers have tabulated the frequency and the type of neurological disease in both Hodgkin's granuloma and sarcoma.

Most of these reported cases of Hodgkin's granuloma have had secondary

involvement of cranial and spinal bones with extension to the dura or an epidural tumor without bone lesions. There have been no well documented cases of this tumor occurring either primarily or secondarily in the substance of the brain. The only possible exception is the case of Von Hecker and Fischer (33) in which there was a granulomatous mass in the centrum semiovale. However, an earlier biopsy of an axillary node had shown a "small round cell sarcoma" and the tumor in many of the organs did not show a clear-cut picture of Hodgkin's granuloma.

From the large number of reported cases and from our own material which has included several in which the diagnosis was established by surgical biopsy certain generalizations can be drawn. Both Hodgkin's granuloma and Hodgkin's sarcoma may cause neurological symptoms. The most frequent lesion is an epidural tumor which compresses the spinal cord. The spinal symptoms may be the first indication of the disease or may develop later. The tumor may extend to the epidural space from adjacent vertebras or from mediastinal and retroperitoneal lymph nodes. The vertebral lesion is of a destructive character in no way different from other lymphomas or from carcinoma. The tumor tissue is firm, grayish pink to yellowish white and, as a rule, does not penetrate the dura. The thoracic vertebras are involved most often and next in frequency are the cervical and lumbosacral. The usual symptoms are those resulting from spinal cord compression i.e. motor and sensory paralysis below the level of the lesion. As a rule the course of the disease, which varies from 2 to 15 years, is shortened considerably by the advent of spinal paraplegia though isolated cases have survived for a year or two following this event. Cranial bones and the neighboring dura are less often the site of Hodgkin's granuloma. Usually the bones of the base of the skull are invaded directly by tumor in the nasopharynx or cervical lymph nodes. Cranial nerves are implicated but the brain is usually not compressed to any significant degree. Invasion of the substance of the brain, if it occurs at all, is rare.

Although we have seen several cases of Hodgkin's granuloma with spinal paraplegia in the last few years none of them have come to autopsy. In this same period of time postmortem examinations of 21 cases of Hodgkin's granuloma have been performed and in none of them was the nervous system involved.

The following case was chosen from the surgical files and is presented here because it exemplifies the clinical neurological aspects of this disease.

Case 6. (S-38-3776) Male, 42 years old: The patient entered the hospital because of progressive weakness of the legs and difficulty in controlling urine of one month's duration. Prior to the onset of these symptoms he had enjoyed good health.

The temperature was 101°. There were several skin lesions, said to have been suggestive of "lymphoblastoma". Several large firm cervical lymph nodes were present. The spleen and other abdominal viscera were not palpably enlarged. There was a flaccid paraplegia and weakness of the abdominal muscles. The abdominal reflexes were absent and the knee and ankle jerks were very feeble; the plantar reflexes were extensor bilaterally. Pain sensation was impaired from 5th thoracic to the 1st lumbar segments and below this level all forms of sensation both superficial and deep were almost absent.

The red cell count was 4,300,000 and the hemoglobin was 85 per cent; the white cell count was 7,300 and the smear was normal. There were a few white blood cells and a trace of

albumen in the urine. A lumbar puncture revealed a complete dynamic block and a fluid which was slightly yellow, with a protein of 258 mg., two lymphocytes per cu. mm., a gold sol curve of 5544433200 and a negative Wassermann reaction. The x-rays of spine were negative.

A midthoracic laminectomy was done and in the epidural space beneath the lamina of the 6th thoracic vertebra a mass of soft grayish-pink tissue which compressed the spinal cord was found. It apparently had extended along the intervertebral foramens from the posterior mediastinum. Most of the tumor within the spinal canal was removed. After the operation the patient developed decubitus ulcers and a bladder infection. These were finally controlled and x-ray therapy was given. At the time of discharge two months later there had been no improvement in the neurological symptoms.

Diagnosis: Hodgkin's granuloma with involvement of skin, cervical lymph nodes, mediastinum and spinal epidural space; spinal cord compression.

Comment: The subacute course of the spinal cord involvement was entirely consistent with a compression by a malignant tumor. The evidence of generalized lymphadenopathy and the skin lesions supported the possibility of Hodgkin's disease. The absence of a vertebral lesion may have accounted for the painless nature of the illness.

We have not encountered, either among the autopsied cases or our surgical biopsy material, a Hodgkin's granuloma arising in the substance of the brain or spinal cord or involving the brain as a metastasis.

HODGKIN'S SARCOMA OF BRAIN AND SPINAL CORD

Hodgkin's sarcoma is a rapidly growing and highly malignant tumor. Although the histological features of this tumor should be sufficiently distinctive to permit diagnosis, it is not always recognized when the tumor occurs in an unusual location. As a consequence, confusion has arisen in the classification of many cases of Hodgkin's sarcoma and it is therefore impossible to judge its frequency from published reports. Examples of reticulum cell sarcoma and probably of Hodgkin's sarcoma can be found among tumors classified as medulloblastoma, round cell sarcoma and perithelial sarcoma or perithelioma. In our pathological material transition from Hodgkin's granuloma to sarcoma was infrequent and the reverse did not occur. The tumor has usually remained true to type from the onset to the termination of the disease.

In most of the articles on Hodgkin's disease of brain and spinal cord, no distinction was drawn between granuloma and sarcoma. Examples of Hodgkin's sarcoma of the spinal epidural space have been reported by Jackson and Parker (32). In these cases, as in lymphosarcoma and Hodgkin's granuloma, there was secondary involvement of nervous structures; the tumor either metastasized to the dura by way of the blood stream or had extended along the intervertebral foramens directly to the epidural space. The tumor did not penetrate the dura but effected a compression from without.

Grossly these tumors appear whitish, or grayish pink, are homogeneous or mottled, and are firm in some cases and exhibit areas of softening in others. In the spinal epidural space one or several flattened masses of tumor compress the spinal cord. The vertebras, as in granuloma, may or may not be involved. However, since primary Hodgkin's sarcoma of bone has not been reported, in those cases with vertebral destruction one expects to find lymph node or visceral

involvement. Life expectance is not more than 1–2 years and is greatly decreased by spinal paralysis.

In our pathological material there were 19 autopsied cases of Hodgkin's sarcoma. Of these 2 had spinal cord compression and 3 had a solitary brain lesion. The following are typical cases of Hodgkin's sarcoma with spinal cord compression.

Case 7. (A-36–495) Male, 52 years old: Two months before admission this patient began to have sharp pains in the lower part of the chest on the right side. These pains increased in severity. Three weeks later his legs gradually became weak and numb. The weakness progressed and at the time of entry to the hospital he was barely able to walk.

The patient was afebrile and his nutrition and color were good. He had a loose but nonproductive cough. His breathing was diaphragmatic. The upper extremities, especially the hands, were weak. He was unable to sit up or turn himself in bed. The motor power in the legs was greatly reduced. The muscles were hypotonic but not wasted. Tendon reflexes in the arms and legs were barely elicited and the plantar reflexes were extensor bilaterally. There was slight impairment of pain and touch sensation from 3rd cervical to 10th thoracic dermatomes bilaterally but sensation in the lower extremities was normal. The lymph nodes were not enlarged and the liver and spleen were not palpable.

The hemoglobin was 77 per cent, the red cell count was 3,800,000 and the white cell count was 5000 with a normal smear. The urine was normal. X-rays of the spine revealed slight hypertrophic arthritis. The cerebrospinal fluid was yellow with 4+ Pandy reaction; the dynamics were impaired; there were no cells and the Wassermann reaction was negative.

During the first few days in the hospital the patient's condition declined rapidly. His temperature rose to 104° and he died.

Anatomical Diagnoses: Hodgkin's sarcoma involving thoracic wall, posterior mediastinum, periaortic lymph nodes, liver, testicle, bone marrow, and spinal epidural space; spinal cord compression.

Comment: At autopsy there was soft gray, friable tumor in the form of flattened nodules over the dorsal and lateral surfaces of the cervical and thoracic cord (C3 to T11). These tumor masses were continuous through the thoracic inter-vertebral foramens with tumor tissue in the posterior mediastinum. The vertebral bones and the dura were not invaded. The spinal cord was compressed from the 3rd to 6th cervical segments.

Case 8. (A-44–585) Female, 59 years old: Approximately 11 months before admission the patient began to have pain between the shoulder blades. It was of dull aching, sometimes sharp character and was limited to the region of the thoracic spine. At times it would subside for a few hours. It was not influenced by posture or activity. The pain gradually became more steady and intense. After 5 months she first experienced sharp stabs of pain over the anterior surface of the right thigh. One month before entry the left leg became weak and because of this she was admitted to the hospital. She had lost 28 lbs. in the past year.

The patient was thin and poorly nourished. There was a flaccid paralysis of the left leg and marked weakness of the right leg. The abdominal muscles were weak. The abdominal reflexes and the knee jerks were absent and the ankle jerks could barely be obtained. There was impairment of pain sensation below the 9th thoracic vertebra except in the right foot and the back of the right thigh and calf. Sensation of touch was diminished but the level was lower and not well defined. Vibratory and postural senses were absent in both legs. She was incontinent of urine and feces. There was tenderness over the 6th to 10th thoracic spine and a slight scoliosis of the lower thoracic spine. The liver and spleen were not palpable and there was no significant enlargement of lymph nodes.

In x-rays of the thoracic spine there was "wedging" and partial collapse of the 12th thoracic and 2nd lumbar vertebra. The hemoglobin was 69 per cent and red cell count was 3,300,000; the white cell count ranged from 10–13,000 with a slight polymorphonuclear

leucocytosis. Total blood proteins were 5.4 gms. and the calcium, phosphorus and phosphatase levels were normal. The urine contained many red blood cells, clumps of leucocytes and bacteria (E coli on culture). The cerebrospinal fluid was xanthochromic, clotted spontaneously and had a protein of over 1000 mg.; a complete dynamic block was found; there were no cells and the Wassermann test was negative.

Within a few days after entering the hospital there was a flaccid paralysis of both legs. The condition of the patient was so poor that a laminectomy was considered to be inadvisable. A punch biopsy of the 12th thoracic vertebra was attempted but only a small piece of necrotic tissue was obtained. During the next two months x-ray treatment was given. The patient ate poorly, developed large decubitus ulcers. The urine continued to be infected with B Proteus and E Coli. She died 3 months after entering the hospital.

Anatomical Diagnoses: Hodgkin's sarcoma with involvement of retroperitoneal tissues, thoracic and lumbar vetebrae and spinal epidural space; spinal cord compression; rheumatic heart disease with mitral stenosis.

Comment: Several physicians were of the opinion that this patient had metastatic carcinoma of the thoracic spine with compression of the thoracic segments of the spinal cord. X-rays of the spine were not definitive. Only after failing to find a primary tumor was the unsuccessful punch biopsy attempted. At autopsy a large mass of grayish white, rather soft tumor was found in the retroperitoneal tissues which had invaded the right kidney, the right psoas muscle, the thoracic and lumbar vertebrae and the spinal epidural space. In contrast to case 7, in which the neurological symptoms developed within 2 months, the course of the disease was much slower. Invasion of the spinal epidural space appeared to be secondary to involvement of vertebral bodies.

The possibility of Hodgkin's sarcoma arising within the substance of the brain or spinal cord has been hypothecated but no proved examples had been reported until 1946 when Sparling and Adams (34) described such a case. We had previously seen 2 clinically studied cases in which the only known lesion was in the brain stem or cerebellum but in each instance the autopsy was restricted to the head. Therefore it was impossible to prove that the tumor did not arise in some other organ. Since the case of Sparling and Adams was selected from the material that is more extensively reviewed elsewhere (34), we have summarized it and, also, the 2 incompletely autopsied cases below.

Case 9. (A-45-255) Male, 53 years old: Approximately 3 months prior to entering the hospital the patient began to be drowsy and, at times, confused. These symptoms, at first intermittent, became more pronounced and persisted and were succeeded by a speech difficulty which consisted of slowness and difficulty in finding the correct words. Six weeks later he collapsed while at work and thereafter had a severe headache and an unsteady gait. Weakness of the right arm and leg developed soon afterwards. Several times at night, while asleep, his wife noted jerking movements of his arms and legs. Increasing confusion, nausea and vomiting led to his entry to the hospital.

The temperature, pulse, respirations and blood pressure were all within normal limits. The patient was drowsy and unable to give a satisfactory history. He was inattentive and forgetful and responded to all stimuli slowly and inadequately. There was a spastic right hemiparesis affecting face, arm and leg. The tendon reflexes on the right side were more active than those on the left; the right abdominal reflexes were absent; the right plantar reflex was extensor and the left one flexor. The visual fields and optic fundi were normal and there was no impairment of cutaneous sensation. The liver was enlarged, the lower edge being 7-8 cm. below the costal margin.

The hemoglobin was 80 to 90 per cent. The white blood count and the smear were normal. The fasting blood sugar was 180 mg. per 100 cc. The blood Hinton test was negative. Cere-

brospinal fluid was under normal pressure; it contained 10 lymphocytes per cubic mm. and 333 mg. of protein per 100 cc.; the colloidal gold reaction was 5555443321 and the Wassermann and Davies-Hinton tests were negative. No abnormalities were seen in x-rays of the skull, spine, chest, pelvis and proximal portions of the long bones. In an electroencephalogram, taken on the 9th hospital day, there were 6 to 8 per second waves in all leads, and evidence of marked asymmetry between the two hemispheres especially the left and right frontal lobes, the lower voltage and less regular activity being over the left frontal lobe.

During the first 8 days in the hospital the patient's condition became much worse. He was more confused and was unable to find the correct words to express himself or to comprehend spoken words clearly. The right arm and leg became weaker and more spastic. There was impairment of pain and touch sensation over the right side of the body. He was incontinent of urine and feces.

On the 10th hospital day a ventriculogram was done which disclosed slight displacement of the lateral and third ventricles to the right and obliteration of the anterior horn of the left lateral ventricle. After this procedure the patient became comatose. Two days later a craniotomy was done. The dura was tense and when reflected exposed a firm, grayish white nodule in the superior frontal convolution approximately 2.0 cm. from the frontal pole. The anterior portion of the left frontal lobe was resected. After operation the patient remained in coma. Gradually his temperature rose, blood pressure fell, breathing became stertorous and he died on the 5th postoperative day.

Anatomical Diagnosis: Primary Hodgkin's sarcoma of the brain, left frontal lobe; acute purulent pachymeningitis, leptomeningitis and localized bacterial encephalitis, postoperative; and alcoholic cirrhosis of the liver.

Comment: Clinically this case was regarded as one of either glioblastoma multiforme or secondary carcinoma of the left frontal lobe. The pathological findings therefore came somewhat as a surprise. The surgical specimen consisted of a firm grayish-white mass of tissue, measuring 2 × 2 × 1.5 cm., which was embedded in edematous brain tissue. On cut surface the mass was flecked with minute red and yellow areas. In microscopic sections under low magnification the tumor presented many well preserved areas separated by broad bands of necrotic tissue. The viable tumor consisted of sheets of cells whose diameter was approximately 15μ, lying in no apparent relationship to one another and forming loosely arranged groups and clusters. The viable cells lay near the blood vessels. The nuclei of the tumor cells were large, round to ovoid, and contained moderately coarse, evenly dispersed particles of chromatin. From 1-3 prominent nucleoli were visible. The cytoplasm was relatively sparse. Single lobulated, binucleated and multinucleated giant cells were abundant. There were numerous mitotic figures. No glial fibrils were seen. There was an abundance of reticulum in the form of a network of fibers which surrounded single cells and small clusters of cells. Sparsely scattered collagen fibers were found throughout the tumor. (Fig. III a and b) A complete necropsy and postmortem x-rays of the skeleton revealed no evidence of tumor elsewhere.

Case 10.[1] (NP41-90) Male, 65 years old: The patient was admitted to the neurological service in a stuporous condition. Six months prior to admission following a fall from a ladder he complained of severe pain in his neck and back. He remained away from work for four months and upon his return, he found that he was unable to perform his duties. About five weeks before admission he became ataxic. This grew progressively worse until he was confined to bed. He developed incontinence of urine and feces. Ten days before admission he had difficulty in swallowing and his speech became slurred. He became more confused and stuporous until the time of admission.

Upon examination the patient was a well developed and poorly nourished man who appeared chronically ill. His pupils were equal and reacted well. There was weakness of the right external rectus muscle and a coarse horizontal nystagmus on looking to either side. The corneal reflexes were absent. The entire right side of the face was paralyzed.

[1] Case previously summarized by Jackson and Parker, N. E. J. M. 233: 369, 1945.

He could swallow only with great difficulty and the gag reflexes were absent. His voice was weak and his speech slurred. There was an ataxia of the arms and legs, more marked on the right. No definite sensory impairment could be detected. The deep tendon reflexes were hypoactive and equal. The abdominal and cremasteric reflexes were absent. An equivocal Babinski was elicited on the right.

Urinalysis was within normal limits. The hemoglobin concentration was 85 per cent and the white blood cell count was 10,900 to 17,000. The blood Hinton test was negative. The non-protein nitrogen was 30 mg. per 100 cc. Examination of the spinal fluid revealed an initial pressure of 60 mm. of water, 40 lymphocytes per cubic mm. and 189 mg. of protein per 100 cc. The Pandy test was two plus. The spinal fluid Hinton and Wassermann tests were negative and the gold sol curve was 000123321. X-rays of the skull revealed no abnormalities and x-rays of the cervical spine showed only a moderate hypertrophic arthritis.

Throughout his hospital stay the patient'a condition became steadily worse. Stupor deepened and he became comatose. His temperature, pulse and respirations rose terminally and he expired on the twenty-fifth hospital day in spite of supportive therapy.

Anatomical Diagnosis: Hodgkin's sarcoma of pons and cerebellum.

Comment: The neurological signs indicated clearly a lesion in the pons and cerebellum, chiefly on the right side. The differential diagnosis lay between tumor and abscess with most of the clinical data favoring the former. There was no clinical or radiological evidence of tumor in other parts of the body. At necropsy only the brain was examined. The leptomeninges and dura were not remarkable. The pons as viewed from the ventral aspect was unusually broad and the right half was 0.4 cm. wider than the left. Horizontal section disclosed a soft gray tumor mass occupying the white matter of the right cerebellar hemisphere, the right middle cerebellar peduncle and the tegmentum of the pons on the right. The tumor measured 3.2 by 3.4 centimeters in its largest horizontal diameter. It extended posteriorly to reach the leptomeninges of the cerebellar cortex and medially to the fourth ventricle. The fourth ventricle was almost obliterated by the enlargement of the right cerebellar hemisphere. The lateral and third ventricles were dilated to about twice their normal size and the aqueduct of Sylvius was also dilated. A slight cerebellar pressure cone was noted. Histologically the tumor was a typical example of Hodgkin's sarcoma.

Case 11. (S-42-59) Male, 70 years old: The patient entered the hospital complaining of unsteadiness in walking and double vision of four weeks duration. The ataxia developed insidiously and progressed slowly. After 3 weeks diplopia appeared, the left image appearing above and to the left of the right image.

Physical examination revealed a well-developed and well-nourished elderly white male who was very apprehensive. The pupils were equal and reacted well. Corneal opacities prevented satisfactory visualization of the optic discs. There was weakness of the left superior and internal rectus muscles of the left eye above the horizontal plane and a slight ptosis of the eyelid. During the Romberg test he tended to fall to the left, and in walking he kept his feet wide apart.

Examination of the peripheral blood was not remarkable. The blood Hinton was negative. The spinal fluid drawn on the second hospital day was under a pressure of 150 millimeters of water; dynamics were free; there were 50 lymphocytes and 200 red blood cells per cubic mm. and 160 mg. of protein per 100 cc. The spinal fluid Hinton was positive and the spinal fluid Wassermann was negative. The gold sol curve was 000123221. Repeated examinations of the spinal fluid showed no significant variation from the original findings. X-rays of the skull and chest revealed no abnormalities. X-rays of the spine and pelvis showed only advanced hypertrophic arthritis. An electro-encephalogram taken on the eighth hospital day was said to be normal.

Throughout his hospital stay the patient tended to minimize his symptoms. On the tenth hospital day he was nauseated and vomited repeatedly. A definite facial weakness was apparent on the fifteenth hospital day and two days later weakness of the left arm and leg was noted. On the twentieth hospital day he requested to be discharged. One week later the left hemiplegia was more complete and two weeks following discharge a stiff

neck, difficulty in swallowing and deviation of the protruded tongue to the left were noted. At that time he entered another hospital where a bilateral trephination and an occipital craniotomy were performed. No tumor was found. Post-operatively he failed rapidly and died.

Anatomical Diagnosis: Hodgkin's sarcoma of the cerebellum and corpus callosum.

Comment: The autopsy was limited to the head. The surface of the brain appeared flattened but there were no herniations of either the temporal lobes or the cerebellum. A mass of soft gray tissue with indistinct margins was found in the white matter of the left cerebellar hemisphere and extending across the midline to the right. It measured 4 centimeters in its greatest diameter. The left dentate nucleus and middle cerebellar peduncle were replaced by tumor. Another smaller tumor nodule 2.3 cm. in diameter was found in the splenium and posterior portion of the body of the corpus callosum. Microscopically the tumor was characteristic of Hodgkin's sarcoma. It had infiltrated the meninges in several places.

That the brain was the site of origin in Case 9 seems indisputable. There was no clinical evidence of involvement of cervical lymph nodes, of paranasal sinuses or the nasopharynx, other viscera or bones. Finally, postmortem x-ray of all the long bones and a complete autopsy failed to show tumor in other organs from which a cerebral metastasis could have arisen.

The precise cell type of Hodgkin's sarcoma is not definitely known. Some authorities believe that both Hodgkin's sarcoma and reticulum cell sarcoma are derived from the reticulum cell or histiocyte and differ from one another only in minor details. In other words these tumors are essentially two forms of a histiocytic sarcoma. If this assumption is correct Hodgkin's sarcoma of the brain would be expected to arise from histiocytes of the meninges or adventitia of the blood vessels. A third hypothetical source would be the microglial cells which according to the studies of Hortega (35) are derived during fetal life from histiocytes at certain fixed points in the leptomeninges.

RETICULUM CELL SARCOMA OF BRAIN AND SPINAL CORD

As early as 1913 Ewing (36) suggested the possibility of a tumor derived from the reticulum cells of lymph nodes but Roulet (37) in 1930 was the first to clearly delineate a tumor of this type. He called it "retothelsarkom" and in the United States the terms reticulum cell sarcoma, large round cell sarcoma or lymphosarcoma of the reticulum cell type have been affixed to it. Not all writers are agreed as to the cell of origin. Some hypothecate a reticulum cell and others a histiocyte, clasmatocyte or a pluripotential cell from primitive mesenchyme. The reticulum cell sarcoma most often arises in lymph nodes and has therefore been classed as a lymphoma but inasmuch as cells of this series occur in almost all organs and tissues it is not surprising that it may arise elsewhere. The next most common primary sites are bone, gastrointestinal tract and spleen.

Jackson and Parker (1) have presented an account of the clinical and pathological features of this type of tumor. They view the reticulum cell as identical with the histiocyte, clasmatocyte, macrophage or large wandering mononuclear cell, being derived from mesenchyma and appearing during embryonic life at about the same time as the fibroblast. These cells are believed to occur not only in lymph nodes but in all tissues. The central nervous system representative is the

microgliocyte. The reticulum cell is regarded as a separate entity as distinct as the lymphocyte, fibroblast or smooth muscle cell and is not, as some authors believe, derived from a lymphocyte. Tumors arising from the reticulum cell are designated as reticulum cell sarcomas and those from the lymphocyte as lymphosarcomas. These authors criticize the tendency to classify reticulum cell sarcoma as one type of lymphosarcoma, believing that they differ as to histogenesis, cell type, and pathological and clinical characteristics. The most important differences are: "A number of cases of lymphosarcoma are accompanied by a blood picture of lymphatic leukemia. This is never seen in reticulum cell sarcoma. Reticulum cell sarcoma forms one group of primary bone tumors—whereas true lymphosarcoma is not primary in bone. The age incidence of lymphosarcoma shows two peaks; one in the first, the other in the sixth decade. Generalized reticulum cell sarcoma arising in lymph nodes, on the contrary, occurs in the fifth, sixth and seventh decades. The type cell of the lymphosarcoma is the lymphocyte, that of the reticulum cell sarcoma, the reticulum cell."

In their series of 24 autopsied cases of reticulum cell sarcoma exclusive of bone (occurring among 17,459 autopsies at Boston City Hospital) 14 arose in lymph nodes, 6 in the gastrointestinal tract, 1 in the tonsil, 1 in the spleen and 2 in the brain. The tumor had directly extended to or metastasized to the liver in 10 cases, the pancreas in 9 cases, spleen in 8 cases, adrenal glands in 7 cases, lungs in 6 cases, heart in 5 cases. The disease was preponderant in patients of older age groups (84.5 per cent were over 40 years of age), though exceptional cases of reticulum cell sarcoma of bone occurred during childhood or adolescence. Both sexes were about equally affected. The average duration of life was 3.6 years.

The first case of a primary reticulum cell sarcoma of brain was described by Bailey (38) in 1929 under the name perithelial sarcoma. In 1938 Yuile (39) reported a case from our laboratory which he called microglioblastoma or reticulum cell sarcoma and in the same year another case was described by Ferens (40). Hsu (41) in 1940 presented a second case of perithelial sarcoma from Bailey's laboratory and Benedek and Juba (42) in 1941 reported a tumor of the same type which they called a microglioma. All of these cases including those of Fried (43) in 1926 and Mage and Scherer (44) in 1937 were analyzed by Kinney and Adams (45) who in 1943 presented two additional cases.

The cell of origin within the central nervous system cannot be determined from the available evidence at present. Theoretically it is possible that the meningeal or perithelial histiocyte, the microglial cell or its progenitor, or a primitive reticulum cell, may give rise to a reticulum cell sarcoma. The proof of the exact histogenesis must await further embryological evidence as to the exact origin of the microglial cell. We prefer at present to class this tumor as a reticulum cell sarcoma rather than microglioma or microglioblastoma.

The following 2 cases are typical examples of primary reticulum cell sarcoma of the brain.

Case 12 (A-41-389) Male, 66 years old: The patient was unable to give an accurate account of his illness, but from various sources it was learned that he had been suffering from headaches and had been excessively irritable during the previous two months. On one occasion, two weeks before admission to the Boston City Hospital, he suddenly became faint and

TABLE III

Summary of cases of reticulum cell sarcoma of brain verified by autopsy

AUTHOR	AGE, SEX	SURVIVAL TIME	SYMPTOMS	SIGNS	LOCATION	GROSS APPEARANCE	MICROSCOPIC APPEARANCE
		Mo.					
Bailey	45 M	14	Headache; convulsions; aphasia	Papill-edema; left hemiparesis	Right temporal lobe	No gross description	Small round cell with moderate cytoplasm; abundant reticulum; perivascular tumor cells
Ferens	36 M	16	Headache; nausea and vomiting	Papill-edema; right hyper-reflexia	Left temporal lobe	Gray-red; firm; adherent to dura	Cells resembling histiocytes; abundant reticulum; perivascular tumor cells
Benedek	34 M	1	Headache; failing vision	Right hemiparesis	Left temporal lobe	Yellow-pink; homogeneous	Cells resembling microglia cells; abundant reticulum
Yuile	50 M	1	Headache and drowsiness	Left hemiparesis	Right temporal lobe	Gray-pink; firm	Cells 12–14 microns in diameter; many mitoses; cells resembling microglia; abundant reticulum; perivascular tumor cells
Hsu	9 M	6	Headache; loss of memory; diplopia	Papill-edema; palsy of right side of face; dysarthria	Left temporal lobe	"Fleshy" rubbery consistence; hemorrhage and necrosis	Round and oval cells; abundant reticulum; perivascular tumor cells
Kinney and Adams	72 M	6	Headache and irritability	Confusion; left hemiparesis	Right temporal lobe	Firm; pink-gray; homogeneous	Cells 12–14 microns in diameter; ameboid activity; abundant reticulum; perivascular tumor cells
Kinney and Adams	66 M	3½	Headache and fatigability	Stupor; aphasia; right hemiparesis	Left temporal lobe	Firm; pink-gray; homogeneous	Cells 12–14 microns in diameter; ameboid activity; abundant reticulum; perivascular tumor cells

dizzy. On the night before admission he was arrested by the police, who found him staggering about in the street. It was noticed that he was not drunk but was confused and irrational.

At the time of admission the temperature, respiratory rate, pulse rate and the blood pressure were normal. The patient was well developed and fairly well nourished. He was confused and disoriented in all spheres. Cooperation during the examination was poor. Tests for aphasia showed that he was unable to carry out complicated commands. There was a tendency to perseverate. He could read individual letters and simple words but was unable to comprehend their meaning. He had difficulty in naming common objects and was unable to write. The optic fundi, pupillary reactions, extraocular movements and functions of the rest of the cranial nerves were within normal limits. There was no in-

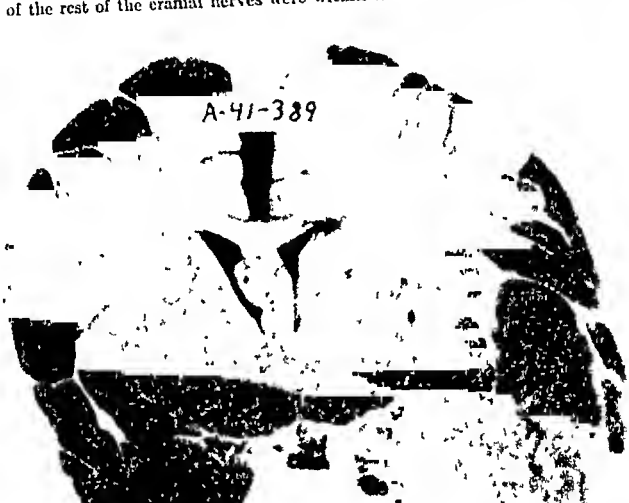


FIG. VII. (CASE 12.)—RETICULUM CELL SARCOMA OF THE LEFT TEMPORAL LOBE

coordination in movements of the arms or legs. Painful stimuli were felt equally well on the two sides of the body, but the confused sensorium prevented more accurate sensory tests. Tendon reflexes were active and equal on the two sides, and plantar responses were bilaterally flexor in type.

The hemoglobin concentration was 76 per cent; the red blood cell count, 3,950,000, and the white blood cell count, 7,650. The Hinton reaction of the blood was negative. The non-protein nitrogen was 30 mg per 100 cc. Urinalysis revealed nothing abnormal except for the presence of a small amount of albumin. Studies of the cerebrospinal fluid revealed a pressure of 100 mm. of water; 31 lymphocytes per cubic mm., and 166 mg. of protein, 60 mg. of sugar and 708 mg. of chlorides per 100 cc. The colloidal gold curve was 0010000000, and the Wassermann reaction was negative.

While in the ward the patient gradually became stuporous. On the twelfth day in the

TABLE III

Summary of cases of reticulum cell sarcoma of brain verified by autopsy

	AGE, SEX	SURVIVAL TIME	SYMPTOMS	SIGNS	LOCATION	GROSS APPEARANCE	MICROSCOPIC APPEARANCE
	45 M	*Mo.* 14	Headache; convulsions; aphasia	Papill-edema; left hemipa-resis	Right tem-poral lobe	No gross descrip-tion	Small round cell with moderate cytoplasm; abundant re-ticulum; peri-vascular tumor cells
	36 M	16	Headache; nausea and vom-iting	Papill-edema; right hy-per-re-flexia	Left tem-poral lobe	Gray-red; firm; ad-herent to dura	Cells resembling histiocytes; abundant re-ticulum; peri-vascular tumor cells
k	34 M	1	Headache; failing vision	Right hemipa-resis	Left tem-poral lobe	Yellow-pink; ho-mogene-ous	Cells resembling microglia cells; abundant re-ticulum
	50 M	1	Headache and drowsi-ness	Left hemi-paresis	Right tem-poral lobe	Gray-pink; firm	Cells 12–14 mi-crons in diam-eter; many mi-toses; cells resembling mi-croglia; abun-dant reticulum; perivascular tu-mor cells
	9 M	6	Headache; loss of memory; diplopia	Papill-edema; palsy of right side of face; dysar-thria	Left tem-poral lobe	"Fleshy" rubbery consist-ence; hemor-rhage and ne-crosis	Round and oval cells; abundant reticulum; peri-vascular tumor cells
ey and ams	72 M	6	Headache and irri-tability	Confusion; left hemipa-resis	Right tem-poral lobe	Firm; pink-gray; homoge-neous	Cells 12–14 mi-crons in diam-eter; ameboid activity; abun-dant reticulum perivascular tumor cells
ey and lams	66 M	3½	Headache and fa-tigability	Stupor; aphasia; right hemi-paresis	Left tem-poral lobe	Firm; pink-gray; homoge-neous	Cells 12 crons eter; dant peri

dizzy On the night before admission he was arrested by the police, who found him staggering about in the street It was noticed that he was not drunk but was confused and irrational

At the time of admission the temperature, respiratory rate, pulse rate and the blood pressure were normal The patient was well developed and fairly well nourished He was confused and disoriented in all spheres Cooperation during the examination was poor Tests for aphasia showed that he was unable to carry out complicated commands There was a tendency to perseverate He could read individual letters and simple words but was unable to comprehend their meaning He had difficulty in naming common objects and was unable to write The optic fundi, pupillary reactions, extraocular movements and functions of the rest of the cranial nerves were within normal limits There was no in-

FIG VII (CASE 12)—RETICULUM CELL SARCOMA OF THE LEFT TEMPORAL LOBE

coordination in movements of the arms or legs Painful stimuli were felt equally well on the two sides of the body, but the confused sensorium prevented more accurate sensory tests Tendon reflexes were active and equal on the two sides, and plantar responses were bilaterally flexor in type

The hemoglobin concentration was 76 per cent, the red blood cell count, 3,950,000, and the white blood cell count, 7,650 The Hinton reaction of the blood was negative The non protein nitrogen was 30 mg per 100 cc Urinalysis revealed nothing abnormal except for the presence of a small amount of albumin Studies of the cerebrospinal fluid revealed a pressure of 100 mm of water, 31 lymphocytes per cubic mm, and 166 mg of protein, 60 mg of sugar and 708 mg of chlorides per 100 cc The colloidal gold curve was 0010000000, and the Wassermann reaction was negative

While in the ward the patient gradually became stuporous On the twelfth day in the

hospital examination revealed the following additional neurologic signs: bilateral sucking reflexes; right hemiparesis, involving the face, arm and leg; slightly increased tendon reflexes on the right side and questionably so on the left, and urinary incontinence.

A ventriculogram was done on the eighteenth hospital day. Both ventricles filled with air and were noted to be pushed to the right. The anterior horn and the body of the left lateral ventricle appeared to be compressed. An electroencephalogram showed a focus of slow wave activity in the left posterior frontal region.

On the nineteenth day in the hospital the patient's temperature rose to 102.8 F., the pulse rate to 160, the respiratory rate to 42 and the blood pressure to 150 systolic and 90 diastolic. The spinal fluid pressure at this time was 250 mm. of water. He died during the early morning of the twentieth hospital day.

Anatomical Diagnosis: Primary reticulum cell sarcoma of the left temporal lobe.

Comment: At autopsy the white matter of the left temporal lobe was largely replaced by tumor which on cut section was homogeneous, grayish-pink and soft in consistence. Microscopic sections of the tumor showed it to be composed of rather large cells, uniform in size and shape, with round to oval nuclei, and rather scanty cytoplasm. Many tumor cells showed pseudopodic projections. There was an abundant coarse reticulum surrounding individual cells and groups of cells. No tumor giant cells were seen. (Figs. IVa & c and VII).

No tumor was found elsewhere in the body.

Case 13 (A-40-192) Male, 72 years old: Headache, weakness and excessive fatigability of approximately three months' duration were the chief symptoms. At the onset of the illness the patient's wife observed that he was unusually drowsy during the daytime. When walking he appeared to stagger toward the left. A few weeks later he began to talk incoherently and was somewhat confused. The headaches, which had developed recently, were of increasing severity. A few days before entry he became stuporous and lost the ability to speak. There had been a weight loss of several pounds. In the past he had always been in good health. During the past year he had been drinking heavily and once, nine months before admission, while intoxicated, he was beaten about the head by an unknown assailant. His neck had been stiff and painful for several years.

The patient was stuporous and aphasic. He sometimes understood simple spoken commands but at other times responded only to painful stimuli. Occasionally he muttered a single word or phrase. When left undisturbed, and even during the examination, he fell asleep. There was evidence of moderate loss of weight. The pupils were equal in size and reacted well to light and in accommodation and convergence. There was no papilledema. The patient did not notice objects in the left half of the visual field. Bilateral buccal and sucking reflexes were elicited. The neck was rigid, and attempts at flexion evoked pain. The patient was too feeble to walk. The left arm was held in a flexed position and the left leg in extension; both extremities were spastic. There was left hemiparesis, affecting the face, arm and leg. The right arm and leg were rigid, being more so at some times than at others. No definite sensory loss was detected. Tendon reflexes were lively on both sides, being slightly more so on the left; the abdominal reflexes were absent; the left plantar reflex was extensor and the right one was flexor. There was a forced grasping response in the left hand. The patient was incontinent of urine and feces.

The white blood cell count was 5,900; the red blood cell count, 3,900,000 and the hemoglobin concentration 78 per cent. The urine showed a trace of albumin; the specific gravity was 1.021, and the sediment contained 6 to 8 red blood cells and an occasional white blood cell per high power field. The cerebrospinal fluid was clear; there were no cells; the pressure was 150 mm.; the protein was 160 mg. per 100 cc.; the colloidal gold curve was 0112232110, and the Wassermann and Davies-Hinton reactions were negative.

The patient's general condition was unchanged during the first two weeks in the hospital. On the fourteenth day a ventriculogram showed upward displacement and partial obliteration of the midportion of the right lateral ventricle and displacement of both lateral ventricles and the third ventricle to the left.

The next day a craniotomy was performed in the right frontal region, and a tumor was noted deep in the substance of the right temporal lobe. The growth did not extend through the cortex to the meninges. It was fairly well demarcated and easily enucleated. The total specimen weighed about 40 Gm. and was white, homogeneous and firm. The patient never regained consciousness after the operation. He died on the eighth postoperative day, or the twenty-second day in the hospital.

Anatomical Diagnosis: Reticulum cell sarcoma of the brain; bronchopneumonia involving the upper and middle lobes of the right lung.

Comment: The focal neurologic signs i.e. the left hemiparesis, the reflex changes, the visual field defect were undoubtedly due to the tumor in the temporal lobe. The stupor, the sucking and grasping reflexes and the changing rigidity of the extremities could not be assigned to a single lesion. They indicated a widespread disorder of cerebral function which may have been caused by increased intracranial pressure and finally a tentorial pressure cone. At autopsy it was found that all the brain tumor had been removed. Gross and microscopic examination of the viscera, lymph nodes and bones disclosed no tumor tissue.

The histological features of these two tumors were identical in every way to those that occur in the lymph nodes and other organs. In the brain they are rapidly growing highly invasive tumors. All of the reported cases have occurred in the temporal lobe thus accounting for the relatively uniform symptomatology. Headache was an early symptom in every case. Mental disturbances constituted a regular symptom and included in later stages drowsiness and confusion. The average duration of symptoms prior to operation was approximately six months. The period of survival after operation varied from three weeks to one and one-third years, the average being three months.

The preponderance of these tumors in the temporal lobe raises an intriguing problem. As previously stated the microglia, derived probably from meningeal histiocytes, invade the brain from certain fixed points among which are the tela choroidea. It is quite possible that tumors from this group of cells arise from these same points and that the tela choroidea of the temporal horn of the lateral ventricles is the site of origin. Support for this hypothesis would be provided by the finding of similar tumors arising from tela choroidea of the III and IV ventricles and cerebral peduncles. It is interesting to note that one of Hsu's cases which he called alveolar sarcoma and which Bailey (personal communication) believes to be similar to our case 2 arose in the cerebellum. Further confirmation of this hypothesis must await the report of additional cases.

Metastases to the brain from reticulum cell sarcoma of lymph nodes or of other organs did not occur in any of our 18 autopsied cases. There were however 3 autopsied cases of extradural reticulum cell sarcoma which compressed the brain or spinal cord. In one case the tumor had invaded a skull bone and had infiltrated the cranial dura, in 1 it had developed in a body or lamina or a vertebra and had extended to the spinal epidural space and in the third case it reached the spinal epidural space along the intervertebral foramens. A fourth case showed a spinal epidural reticulum cell sarcoma on surgical biopsy and in a fifth case, biopsied at this hospital and autopsied at another hospital, there were metastatic brain lesions. Four of these cases, 1 with secondary brain involve-

ment and 3 with spinal cord compression, are summarized below; the clinical data in the other case were too meagre to be of any value.

Case 14 (Biopsy at BCH, Autopsy 5845 Mass. Gen. Hospital) Female, age 54 years: The patient first consulted her physician in May, 1929, because of generalized weakness and lassitude. She had also noted a small subcutaneous nodule near the sternal end of the right clavicle. The nodule was biopsied at the Boston City Hospital and a diagnosis of reticulum cell sarcoma was made. There was no change in her condition during the following 6 months and then a swelling appeared over the left eye.

Examination at that time disclosed 2 significant findings: there was a slight exophthalmos on the right and a firm movable mass deep in the pelvis. Her hemoglobin was 70 per cent, red cell count 3,500,000, white cell count was 9,000 and no abnormal cells were seen in the smear.

High voltage x-ray treatment was given and the exophthalmos began to recede within a few days. In February, 1930, slight confusion and dizziness were first noted and a small subcutaneous infiltration of the left thigh was discovered. In March, 1930, a difficulty in speech was first noted. Then several Jacksonian seizures which involved the face, arm and leg, in that order, occurred. Headaches were also experienced for the first time. In April, 1930, examination revealed an aphasic disorder consisting of a groping for words and inability to comprehend spoken or written words, papilledema, left homonymous hemianopia, impaired position sense and astereognosis in the left arm and leg. The left parotid gland and lymph nodes in the left axilla were firm and enlarged. The patient became stuporous, then comatose. She died in June, 1930.

Anatomical Diagnoses: Reticulum cell sarcoma of skull (ethmoid, sphenoid and temporal bones) meninges, brain, lymph nodes and adrenal glands; leiomyoma of uterus.

Comment: Apparently the tumor tissue first involved a cranial bone and encroached on the orbit and later extended through the dura and pia-arachnoid to the right temporal, parietal and occipital lobes. The convolutions in these lobes were flattened and their surfaces were a mottled, pinkish tan. On coronal sections of the brain the greater part of the occipital, posterior temporal and inferior parietal lobes were replaced by soft grayish-pink tumor tissue. This was the only case in this material in which a reticulum cell sarcoma of a cranial bone or vertebra had invaded the meninges and underlying nervous structures. Viets and Hunter (27) reported this case in their study of "lymphoblastomas" of the brain.

Case 15. (A-38-340) Female, age 65 years: The patient had been admitted to the hospital several times in the past four years because of anorexia and abdominal pain. It was believed that she had alcoholic cirrhosis and toxic hepatitis due possibly to neoarsphenamine which was being administered as treatment for latent syphilis. On the last admission her spleen was found to be very large. X-rays showed a partial destruction of the 6th and 7th thoracic vertebrae. In the past few months she had had severe pain in the lower thoracic region posteriorly. During the two weeks prior to admission both legs had become numb and paralyzed.

The temperature and blood pressure were normal. The patient was well developed and nourished. Her tongue was smooth and red. The spleen filled the entire left side of the abdomen and the liver was enlarged 4–5 cm. below the costal margin. There was a flaccid paralysis of the legs. Abdominal reflexes, tendon reflexes in the legs and the plantar reflexes were absent. All forms of sensation were greatly reduced or absent below the 6th thoracic segment. There was incontinence of feces and urine.

The hemoglobin was 69 per cent; the red cell count was 3,690,000 and the white cell count was 2,200 with 55 per cent polymorphonuclears, 32 per cent lymphocytes and 13 per cent monocytes.

The patient would not consent to have a lumbar puncture. Large decubitus ulcers formed over the sacrum. Radiation therapy was given but patient failed steadily and died after being in the hospital four weeks.

Anatomical Diagnoses: Reticulum cell sarcoma involving the 9–12 thoracic and 1–2 lumbar vertebrae, the spinal epidural space and retroperitoneal tissues; chronic cholecystitis and cholelithiasis, splenomegaly; pelvic peritoneal endometriosis.

Comment: The lower thoracic and upper lumbar vertebral bodies were nearly completely replaced by firm pale grayish white tumor. In the epidural space there were flattened masses of tumor tissue up to 0.4 cm. in thickness and firmly attached to dura. The spinal cord beneath the tumor was pale and extremely soft.

Case 16. (S-34-2327 and A 34-401) Male, age 42 years: The patient, an Italian laborer, was working each day enjoying good health until three weeks before entry at which time he first noticed a dull aching pain in the lower thoracic and upper lumbar spine. This increased in severity until he was unable to work. Two weeks later, when attempting to walk to the bathroom, he discovered that his right leg was weak. Three days later the left leg was similarly affected so that he was unable to walk. During this time numbness and tingling extended over both legs and the abdomen, below the umbilicus. The legs quickly became paralyzed and he lost control of rectal and vesical sphincters.

The patient lay quite helpless in bed unable to sit up or to move his legs. There was pronounced tenderness on percussion of lower thoracic spines. The leg muscles were flaccid. Knee and ankle jerks were slightly exaggerated. The abdominal and plantar reflexes were absent. There was hypesthesia and hypalgesia below the 8th thoracic dermatome. No enlarged lymph nodes were noted and the liver and spleen were not palpable.

The hemoglobin was 98 per cent and the red cell count 5,000,000; the white cell count was 16,800 with 80 per cent polymorphonuclear leucocytes. The urine was negative. Lumbar puncture showed a complete dynamic block; the fluid was xanthochromic and contained 45 white blood cells per cubic mm. and 510 mg. of protein per 100 cc.; colloidal gold was 0000012321 and the Wassermann reaction was negative.

On the second hospital day a mid-dorsal laminectomy was performed. On exposure of the dura a mass of granular, purplish-gray tissue was found in the epidural space at the level of the 6th thoracic vertebra. It filled two-thirds of the spinal canal and extended along the ventral and left lateral surface of the dura for 2.0 cm. It was attached to the body and left lamina of 7th thoracic vertebra. The patient's condition was very poor after the operation and on the second postoperative day he developed signs of pulmonary congestion and died.

Anatomical Diagnoses: Reticulum cell sarcoma involving 7th thoracic vertebra and the spinal epidural space; spinal cord compression; bronchopneumonia, early, bilateral; pulmonary infarcts.

Comment: At autopsy no remnants of tumor were found. Probably the tumor arose in the portion of vertebra removed at operation. The spinal cord at this level was soft and microscopic examination showed the effects of acute compression.

Case 17. (S-40-1683) Male, age 71 years: Four months before admission to the hospital the patient began to have sharp "stabbing" pains in his lower back and right leg. The pains radiated down the posterior and lateral surfaces of the right thigh and leg to the foot and were intensified by coughing and straining. Within a few weeks the strength in both legs began to fail and urgency and precipitancy of urination were noted. He had been confined to his bed for the two weeks preceding hospital entry and suffered greatly from pain. There had been very little weight loss.

The patient was a confused elderly man who was unable to walk without assistance. The muscles of both legs, particularly the anterior tibial and gastrocnemius muscles, were weak and atrophic. The hamstring muscles, the abductor and extensor muscles of the thighs and the gluteal muscles were weak and flabby. The knee and ankle jerks and the plantar reflexes were absent. There was a sensory level at the second lumbar segment below which all sense modalities were greatly reduced or lost. The remainder of the examination was essentially negative. The lymph nodes and spleen were not enlarged.

The hemoglobin was 13.7 gm. per 100 cc.; the red cell count was 4,280,000 and the white cell count was 7,250 with normal smear. The urine was normal. X-rays of spine revealed

partial destruction of the 12th thoracic vertebra. The serum calcium was 9.6 mg. per 100 cc., the phosphorus was 3.4 mg. per 100 cc. and phosphatase was 16.6 Bodansky units. The initial pressure of the cerebrospinal fluid was 110 mm.; there was no rise in pressure with jugular compression; the fluid was yellow and the protein was 3180 mg. per 100cc.; there were no cells and the Wassermann reaction was negative.

A provisional diagnosis of metastatic carcinoma with compression of the lumbar cord was made even though the source of the assumed metastasis was not found. No treatment was given and he returned to his home. During the next four months the pains continued and complete paralysis of bladder and rectum developed. He returned to the hospital and a laminectomy was performed. Tumor tissue was found to have destroyed the laminae and articular processes of 1st, 2nd and 3rd lumbar vertebras. Soft pinkish gray tumor tissue filled the epidural space from the 12th thoracic to the 4th lumbar vertebras. Much of this tissue was removed. After operation pressure sores, bladder infection and pain interfered with convalescence. Radiotherapy was given and at the time of discharge three months later he was quite comfortable without medication but was still bedfast. The final outcome of the case is not known.

Diagnosis: Reticulum cell sarcoma of lumbar and thoracic vertebrae; spinal cord compression.

The syptomatology in these cases with cord compression was quite uniform. Pain in the back, either in the region of spine or radiating over one or two dermatomes was the first symptom and was followed within days to weeks by paresthesias, progressive weakness and ataxia of the limbs below the level of the lesion and by paralysis of bladder and rectum. The duration of symptoms from onset to complete paralysis varied from weeks to 3–4 months. There was a dynamic block, an elevated protein and, in some cases xanthochromia of the spinal fluid. The clinical picture did not differ from that of any other rapidly growing tumor in the spinal epidural space. X-rays of the spine, in those cases in which the tumor arose in the vertebra, showed only a destructive lesion which the radiologist could not distinguish from metastatic carcinoma or Hodgkin's granuloma or sarcoma.

PLASMACYTOMA OF BRAIN AND SPINAL CORD

Multiple myeloma, usually regarded as a malignant tumor arising in the bone marrow, is the best recognized form of this disease. A multiplicity of lesions in flat bones containing red marrow is the outstanding feature. It is quite impossible in most cases to state whether the disease is primary in one focus, the other bony lesions being secondary, or multiple from the beginning. In a few cases, however, a solitary focus in lymph nodes or bones may be present for years before dissemination occurs. These single or localized tumors are designated as plasmacytomas, plasmomas or plasma cell myeloma. The former term is used in our laboratory. In either the plasmacytoma or multiple myeloma the plasma cells may enter the circulating blood, a condition known as plasma cell leukemia, and in about 50 to 60 per cent of cases Bence-Jones albuminuria occurs.

With such extensive involvement of skull bones and vertebrae by a malignant tumor neurological symptoms might be expected to develop in many cases. Geschickter (47) states that neurological symptoms develop in approximately 40

per cent of the cases and that the most important of these is the paraplegia that accompanies myeloma of the vertebral column.

The medical literature is replete with references to cases of paraplegia from multiple myeloma. In these cases there is an epidural tumor arising as an extension from adjacent osseous foci in most instances but occasionally the epidural tumor seemed to develop in the epidural tissues without evidence of a lesion in an adjacent vertebra or elsewhere. Verda's (13) case illustrates the latter form of the disease and one of Browder and de Veer's cases showed no osseous lesions for a year after the removal of an epidural tumor. The chronicity of the disease in some cases is even more strikingly exemplified in the report of 9 cases by Klemme (46) where after surgical excision and deep Roentgen therapy there was survival for three years in 1 and for over 10 years in 2 others.

Occasionally neurologic symptoms have resulted from myelomatous infiltration of the cranial meninges and implication of cranial nerves. However, invasion of the substance of the brain is singularly rare. As with any extensive disease of the bone marrow, brain hemorrhage or thrombosis of veins may occur. Walgren (48) and Venturi (49) have described cases in which the intracranial venous sinuses have become thrombosed and in Venturi's case a thrombosis of the central retinal artery caused complete blindness.

In our pathological material there were 15 autopsied cases and 3 surgical biopsies of multiple myeloma or plasmacytoma. The nervous system was involved in 5 of the autopsied cases. In 2 of the 5 autopsied cases there was a plasmacytoma of the spinal epidural space and spinal cord compression, in 2 cases cranial bones were involved and several cranial nerves were compressed, and in 1 case a diffuse myelomatous infiltration of the meninges occurred. The 3 surgical biopsies were all from spinal epidural tumors. In all of our cases the tumor appeared to have extended from lesions in adjacent bones. In 1 of the cases there was a plasma cell leukemia.

In gross appearance these tumors are soft and gray or red and form discrete masses on the epidural surface of the cord or brain. It is usually not difficult to demonstrate that the tumor is directly continuous with similar lesions in a neighboring bone. The Roentgen appearance is fairly characteristic. Small, discrete areas of rarefaction with rather soft margins can be seen. The lesion is one of rarefaction; new bone formation does not occur.

The 4 cases summarized below exemplify the clinical course and pathology of this disease.

Report of Cases

Case 18. (S-42-4456) Male, age 55 years: The patient entered the hospital with the chief complaint of weakness and heaviness of both legs of 7 weeks duration. The initial symptoms were coldness and numbness first of the right foot, then of the left which slowly spread up the legs to the level of the umbilicus. Associated with the paresthesia there was a weakness of legs, first left then right, which at first caused him to walk slowly and to fatigue quickly but later prevented walking altogether. The urinary stream had become feeble and both urgency and precipitancy of urination had recently occurred. His weight

had been constant. For the past 2 weeks coughing produced pain in the middle of his back.

The patient was a moderately obese man who was oriented and rational. There was slight limitation in forward bending of the upper lumbar spine and slight tenderness and swelling over 8th and 9th thoracic spines. The gait was spastic and ataxic. Both legs were quite weak, the left more than the right, yet the muscles were not wasted. The knee and ankle reflexes were lively, the left more than the right; the abdominal reflexes were absent and the plantar reflexes were extensor. There was sustained ankle clonus on left and unsustained on the right. Senses of vibration and position were impaired belowthe knees. Between 8th thoracic and the 3rd lumbar segments pain sense was reduced in acuity and pin prick felt "like fire". The Romberg sign was present. The liver and spleen were not palpable; there was no enlargement of lymph nodes.

The hemoglobin was 98 per cent, the red cell count 5,100,000 and the white cell count 9,800 with normal differential. Cerebrospinal fluid: there was a partial dynamic block; no cells were present; the total protein was 48 mg. per 100 cc.; Wassermann reaction was negative. X-rays of the thoracic spine revealed erosion of the left pedicle of the 6th thoracic vertebra and slightly increased radiance of the body of this vertebra.

Transfer to the neurosurgical service for laminectomy was arranged but the patient would not consent to the operation. He went home and during the following month his legs gradually became weaker. Three days before re-entry he contracted a respiratory infection. The next day he awakened to find his legs paralyzed. Examination at this time showed greater weakness and spasticity of the legs and hypalgesia and thermohypesthesia below the costal margin, including the sacral segments. Touch sensation was preserved. At this time the hemoglobin was 79 per cent and the red cell count, 4,100,000 but the white cell and differential counts were normal. The total proteins of blood were 6.18 gms. A thoracic laminectomy was performed and exposed a mass of soft pinkish-gray tissue in the spinal epidural space beneath the 6th thoracic vertebra. The laminas, transverse processes, especially the left, and the pedicles were soft and replaced by this tissue. The tumor within the spinal canal was completely removed. The tumor had indented the spinal cord but not infiltrated the dura. A few days after the operation the patient was sitting up and at the time of discharge two weeks later was able to walk unassisted.

Diagnosis: Plasmacytoma of 6th thoracic vertebra and spinal epidural space; spinal cord compression.

Comment: The clinical picture was one of subacute spinal cord compression by a solitary epidural lesion. Unfortunately no information as to the subsequent course of the illness could be obtained.

Case 19. (A-43-235) Male, age 51 years: Five months before admission the patient fractured his left clavicle while removing a heavy box from a high shelf. After this incident his health failed gradually and he began to have a pain along the anterior surface of the left thigh. He limped, favoring the left leg. Three months later his legs became weak and numb. This condition progressed to the point where he was completely paralyzed and lacking in sensation below the waist. He also became incontinent of urine and feces. Two weeks before admission to the hospital he developed fever and a cough which was diagnosed as pneumonia and seemed to respond to sulfonamide therapy.

The patient was an irritable man who was malnourished and of sallow complexion. His breathing was labored. His thinking processes were slow and he was somewhat confused. The tongue was red and dry. There was no percussion dullness over the chest but coarse rales were heard throughout both lung fields. The heart rate was rapid and the sounds were of poor quality. No masses or enlarged viscera could be palpated in the abdomen and the lymph nodes were not enlarged. There was a flaccid paraplegia with diminished tendon reflexes in the legs and absent abdominal and plantar reflexes. All forms of sensation were diminished or absent below the 8th thoracic dermatome.

The white blood count was 43,000 but the differential count was not recorded. The hemoglobin was 45 per cent and the red cell count was 2,100,000. The urine sediment

contained a few red cells and white cells and there was a +++ positive test for albumen (no test for Bence-Jones protein was done). The blood Hinton test was negative. The acid phosphatase was .75 units and alkaline phosphatase was 2.18 units. Cerebrospinal fluid: There was a complete dynamic block; the fluid was slightly yellow and the total protein was 135 mg.; there were 12 lymphocytes per cu. mm.; the gold sol was O^{10}.

The patient's condition became rapidly worse and he died in less than 24 hours.

Anatomical Diagnoses: Multiple myeloma involving the frontal, parietal and occipital bones, vertebras and spinal epidural space, clavicles, ribs, iliums, liver, kidneys, periaortic, hypogastric, left supraclavicular and inguinal lymph nodes; spinal cord compression; meningioma—olfactory groove, left.

FIG. VIII. CASE 19.—PLASMACYTOMA OF THE SPINAL EPIDURAL SPACE AND MENINGIOMA OF THE LEFT OLFACTORY GROOVE

Comment: A pathological fracture of the clavicle was the first event in this illness This of course is indicative of a destructive bone lesion and according to Geschickter and Copeland (50) is much more suggestive of multiple myeloma than of secondary carcinoma. Anemia and albuminuria which are often observed in multiple myeloma were also present. The total protein and albumin-globulin ration of blood were not determined. The neurological symptoms were those of a rapidly growing epidural spinal tumor.

At autopsy a soft grayish mass of tumor tissue extending from vertebral bodies and pedicles was found in the epidural space of the upper thoracic cord. The tumor measured 0.6 cm. in thickness and extended 6.0 cm along the epidural space. The spinal cord was slightly indented but the dura had formed an effective barrier against tumor invasion. (Fig. VIII and Va) Microscopically the tumor was composed of sheets of immature plasma cells with scattered giant cells and multinucleated cells. The cranial dura was infiltrated with plasma cells. (Fig. Vb and c)

There were no symptoms which could be attributed to the meningioma. The olfactory sense and the visual fields were not tested.

Case 20. (A-44-179) Male, age 70 years: Approximately 11 months before entry to the hospital the patient noted the gradual onset of dull pain in the left frontal region of the head. In the course of the next few months it became more intense and extended to the entire left side of his head, especially the post auricular region. An examination in the Out-Patient Clinic was made at this time but the cause of the pain was not determined. Although tinnitus had been present for many years, loss of hearing in the left ear was first noted about 6 months previously and has been progressive since that time. Also, there had been unsteadiness of gait with reeling to the left side. During the month prior to hospital entry swallowing difficulty had developed and the left side of the face had become weak. His voice became hoarse about the same time. There had been no weight loss despite the difficulty in swallowing.

The patient was alert and described his symptoms well. His nutritional state was good. There was a partial paralysis of the left abducens nerve and lateral nystagmus which was greatest on left lateral gaze. Sensation over the left side of the face, both touch and pain, were impaired and the left corneal reflex was absent. The left side of the face was paralyzed and the left ear was deaf both for air and bone conduction. The palate deviated to the right and the voice was hoarse. The tongue deviated to the left and was slightly atrophied on the left side. In walking the patient tended to fall to the left side. The Romberg sign was absent. There was no weakness or ataxia of arms or legs. The tendon reflexes were normal but the left plantar reflex was equivocal and the right one was flexor. Otherwise the physical examination revealed no abnormal findings.

The red cell count was 4,900,000; the white cell count was 7,300 with a normal differential. The cerebrospinal fluid was under a pressure of 180 mm.; there were no cells and the total protein was 80 mg.; Wassermann and Davies-Hinton tests were negative. The urine was normal except for a very slight trace of albumin. In x-rays of skull there was "extensive destruction of the roof of the left internal meatus".

A bilateral suboccipital craniotomy was performed. When the left cerebellar hemisphere was retracted, a firm, encapsulated grayish-pink tumor mass was seen arising from the posterior surface of the petrous bone and compressing the 7th and 8th cranial nerves. By sacrificing the 9th, 10th and 11th cranial nerves part of the tumor was removed. That night the patient's temperature rose to 102°. He died on the second postoperative day.

Anatomical Diagnoses: Plasmacytoma of the sphenoid and both petrous bones with compression of left 5th, 6th, 7th, 8th and 9th cranial nerves; pulmonary edema.

Comment: The neurological symptoms were those of a rapidly growing tumor which implicated the V to IX cranial nerves and compressed the cerebellum. At autopsy a mass of grayish-pink, soft tumor was found in the epidural space where it had extended from the left sphenoid and temporal bones. The left cerebellar hemisphere had been partly resected but it did not appear to have been invaded by the tumor. There was no tumor in other bones or in lymph nodes.

Case 21. (A-46-409) Male, age 66 years: The patient had noticed weakness, excessive fatigability and moderate weight loss for the past year. In the month prior to entry he had developed pain and weakness first in the right arm then, three days later, in the right leg. Also, there had been an acute onset of diplopia and impairment of vision in the left eye. A collapse in the Medical Out-Patient Department led to his hospital admission.

At this time the patient was slightly confused. He appeared very pale but in a fair state of nutrition. The blood pressure was 140/100. There was weakness of the right external rectus muscle. The vision in the left eye was impaired to the point where fingers could be counted at only a distance of one foot. The margins of both optic discs were indistinct. The visual fields and pupillary reflexes were normal. Deep palpation of the right upper arm and right thigh and passive and active movements of the right arm and leg evoked pain. Heavy percussion over lower thoracic spines was very painful. All of the tendon reflexes were present and equal on the two sides of the body. The plantar reflexes were flexor, bilaterally. There were no sensory changes.

The urine contained no albumin or Bence-Jones protein. The red cell count was

2,900,000 and hemoglobin was 56 per cent. The white cell count was 4,700 and the smear was normal; there were no plasma cells. The total blood proteins were 8.1 gms. per 100 cc. with 6.0 gms. of globulin and 2.1 gms. of albumin. The cerebrospinal fluid was under a pressure of 120 mm. of H_2O; there were no cells, the protein was 21 mg., the Wassermann reaction was negative and the colloidal gold was 5555551332. Roentgenograms of skull, spine, ribs and long bones showed multiple small, fairly discrete areas of bone destruction. There were pathological fractures of the right humerus and femur.

While in the hospital the pains gradually subsided with immobilization of the right arm and leg. Vision in the left eye improved and the strabismus became less noticeable. Several blood transfusions were given. The patient died at home five months later.

Final Anatomical Diagnoses: Multiple myeloma involving ribs, right humerus, femurs, pelvis and base of skull; compression of the right abducens nerve; acute and chronic pyelonephritis.

Comment: The sphenoid bone was extensively infiltrated with tumor tissue. The dorsum sellae was soft and grayish-pink on cut surface. The dura over these lesions was intact. The sheath of the abducens nerve was not invaded though the nerve was surrounded by immature plasma cells. The left optic nerve and retina were gressly and microscopically normal. No cause for visual impairment was found. The laminae and pedicles of many of the vertebras were replaced by tumor tissue but the spinal cord was not compressed. The weakness of the right arm and leg were due presumably to the pathological fractures.

DISCUSSION

A. Pathological

Although the number of instances of nervous system involvement by malignant lymphoma is not sufficiently great to warrant dogmatic conclusions at the present time, it appears that certain neuropathological changes are prone to occur in particular types of lymphoma.

Lymphoid tissue is not a normal constituent of the brain and spinal cord. Except in pathological states no more than a few scattered perivascular and meningeal lymphocytes are present. On the other hand both histiocytes, in the meninges and perithelium of brain vessels, and microgliocytes in brain substance are normal cellular constituents of the brain. In the epidural space small collections of lymphocytes are not uncommon and, in addition, blood vessels, connective tissue and fat are found. There is no cranial epidural space, the dura being the inner periosteum.

From these anatomical facts it is reasonable to deduce that those types of lymphoma which are derived from lymphocytes, lymphoblasts and plasma cells should not arise within the brain or in any structure underneath the dura. Furthermore, the tumors which are derived from histiocytes, Hodgkin's sarcoma and reticulum cell sarcoma, might be expected to occur as primary tumors of the brain.

These conclusions seem to be borne out by our pathological material and also by the recorded cases in the medical literature. Involvement of the nervous tissue by lymphosarcoma, plasmacytoma and giant follicle lymphoma is notably infrequent, the nervous symptoms and signs usually being the result of compression of nerve tissue by tumor in the epidural space. The occurrence of reticulum cell sarcoma and Hodgkin's sarcoma within nervous tissue, as pre-

viously postulated, is established beyond doubt by our three cases of Hodgkin's sarcoma and three cases of reticulum cell sarcoma.

In our experience both reticulum cell and Hodgkin's sarcoma of the brain appeared grossly as a discrete mass of soft, grayish-pink tissue. All of the reticulum cell sarcomas were in the temporal lobe, while the Hodgkin's sarcomas were located in the cerebellum, brain stem and frontal lobe. These tumors replaced white matter and occasionally invaded the cortex and pia. The demarcation from adjacent brain tissue was more distinct than in the gliomas and less distinct than in metastatic carcinoma. Localized cerebral edema was usually present but varied in degree. Ventricular displacement, obstructive hydrocephalus and brain herniation were common findings. Extensive invasion of the brain and destruction of brain tissue were evident in microscopic sections. Occasionally the tumor seemed to have spread along perivascular spaces. No metastases were observed to other parts of the nervous system but the spinal cord and especially the cauda equina were not examined in some of the cases.

The existence of primary lymphoma of the spinal epidural space is doubtful. Although cases with isolated epidural lesions of plasmacytoma, lymphosarcoma, Hodgkin's granuloma or giant follicle lymphoma are recorded, the proof for the most part is based on clinical and operative evidence and is not therefore conclusive. In none of our cases was there a proved solitary lesion of the spinal epidural space. One case of localized reticulum cell sarcoma apparently was primary in a vertebra.

Secondary involvement of the nervous system is usually the result of extension from nearby tumor. Metastases from distant foci, while they do occur, are infrequent. In some cases the neurological symptoms may precede symptoms of tumor elsewhere. Involvement of the intracranial dura is usually the result of invasion of tumor through the bones of the base of the skull from lymphomatous masses in the pharynx or cervical lymph nodes. Retroperitoneal, mediastinal or cervical masses may extend into the spinal epidural space through the intervertebral foramens. This is especially true of Hodgkin's granuloma, Hodgkin's sarcoma, reticulum cell sarcoma and less often of lymphosarcoma. Invasion of the spinal epidural space may also result from extension of tumor primarily or secondarily involving the vertebras. This is most frequently seen in reticulum cell sarcoma and plasmacytoma.

The tumors causing cord symptoms were in the spinal epidural space. They were adherent to the periosteum, replaced the epidural fat and either encircled the cord or were situated on one side of it. The vertical extent of the tumor varied; it was limited to one or two segments in some cases and extended the length of the cord in others. The gross appearance of the tumor varied more with the rapidity of growth than with the type of lymphoma; if slowly growing it was firm, whitish and nodular, if rapidly growing, softer, reddish or pinkish-white and necrotic.

The most frequent cause of neurological symptoms in this group of tumors was spinal cord compression. Beneath the greatest mass of tumor tissue the spinal cord was narrowed and pale. On cross section the gray matter was poorly

demarcated from the white matter. The fine vascular ramifications within the pia were obliterated. In a few of the cases, in which the compression was rapid, the spinal cord was extremely soft, even to the point of liquefaction, and the meningeal vessels were congested. This was probably the result of infarction and suggested that ischemia was a relatively important factor in acute and probably also in chronic compression of the spinal cord.

In microscopic sections of the spinal cord there was considerable variation from case to case. The usual findings were small irregularly shaped areas of fenestration occurring in the more superficial parts of the white matter and imparting a cribriform appearance. These vacuolated spaces ranged in size from 25 to 100 μ, and in many of them there was a round homogeneous body, representing a dilated axis cylinder. In more chronic lesions the axis cylinders had disappeared and one or several microglial phagocytes could be seen. Astrocytes were increased in number and size. Sometimes one or two small foci of ischemic necrosis were present and depending on the age of the lesion the tissue was poorly stained and structureless or was replaced by microglial phagocytes. In the acutely necrotic lesions the portion of the spinal cord below the involved segment was completely disorganized. All structures except possibly blood vessels, the connective tissue septa and pia had disappeared and if the lesion was more than a week or two old a pronounced microglial proliferation was present. Proliferation of astrocytes was a later event. Occasionally a thrombosed vein or artery was seen but these were not found with sufficient regularity to account for the deprivation of blood supply.

Infiltration and compression of spinal roots and ganglia occurred in some cases. In lymphosarcoma or lymphatic leukemia tumor cells insinuated themselves between fascicles of nerve fibers and along the perineurium. The exact mechanism of damage was not apparent because similar infiltrations by inflammatory cells, so frequent in a bacterial leptomeningitis, seldom damage nerve fibers. Compression may have been a factor especially when the sensory ganglia and nerves were implicated in the intervertebral foramens. Similarly small masses of tumor cells sometimes infiltrated the meninges. The infiltrating masses were at times so diffuse or so small as to escape detection on gross examination.

B. Clinical

In reviewing our cases and also the case reports in the literature it was striking how often the true nature of the disease escaped recognition until a surgical biopsy or an autopsy was performed. In part this is due to the rarity of lymphomas and especially those associated with neurological symptoms. Seldom does one neurological physician build up a sufficiently large clinical experience to become thoroughly familiar with all aspects of this problem. Another source of error has been the lack of careful neurological examination of patients suffering from lymphomatous diseases. Often these patients were on a medical ward, desperately sick, and were not available to the neurologist.

There are four outstanding clinical syndromes in lymphomatous diseases of the nervous system. The first and most frequently encountered one was that

viously postulated, is established beyond doubt by our three cases of Hodgkin's sarcoma and three cases of reticulum cell sarcoma.

In our experience both reticulum cell and Hodgkin's sarcoma of the brain appeared grossly as a discrete mass of soft, grayish-pink tissue. All of the reticulum cell sarcomas were in the temporal lobe, while the Hodgkin's sarcomas were located in the cerebellum, brain stem and frontal lobe. These tumors replaced white matter and occasionally invaded the cortex and pia. The demarcation from adjacent brain tissue was more distinct than in the gliomas and less distinct than in metastatic carcinoma. Localized cerebral edema was usually present but varied in degree. Ventricular displacement, obstructive hydrocephalus and brain herniation were common findings. Extensive invasion of the brain and destruction of brain tissue were evident in microscopic sections. Occasionally the tumor seemed to have spread along perivascular spaces. No metastases were observed to other parts of the nervous system but the spinal cord and especially the cauda equina were not examined in some of the cases.

The existence of primary lymphoma of the spinal epidural space is doubtful. Although cases with isolated epidural lesions of plasmacytoma, lymphosarcoma, Hodgkin's granuloma or giant follicle lymphoma are recorded, the proof for the most part is based on clinical and operative evidence and is not therefore conclusive. In none of our cases was there a proved solitary lesion of the spinal epidural space. One case of localized reticulum cell sarcoma apparently was primary in a vertebra.

Secondary involvement of the nervous system is usually the result of extension from nearby tumor. Metastases from distant foci, while they do occur, are infrequent. In some cases the neurological symptoms may precede symptoms of tumor elsewhere. Involvement of the intracranial dura is usually the result of invasion of tumor through the bones of the base of the skull from lymphomatous masses in the pharynx or cervical lymph nodes. Retroperitoneal, mediastinal or cervical masses may extend into the spinal epidural space through the intervertebral foramens. This is especially true of Hodgkin's granuloma, Hodgkin's sarcoma, reticulum cell sarcoma and less often of lymphosarcoma. Invasion of the spinal epidural space may also result from extension of tumor primarily or secondarily involving the vertebras. This is most frequently seen in reticulum cell sarcoma and plasmacytoma.

The tumors causing cord symptoms were in the spinal epidural space. They were adherent to the periosteum, replaced the epidural fat and either encircled the cord or were situated on one side of it. The vertical extent of the tumor varied; it was limited to one or two segments in some cases and extended the length of the cord in others. The gross appearance of the tumor varied more with the rapidity of growth than with the type of lymphoma; if slowly growing it was firm, whitish and nodular, if rapidly growing, softer, reddish or pinkish-white and necrotic.

The most frequent cause of neurological symptoms in this group of tumors was spinal cord compression. Beneath the greatest mass of tumor tissue the spinal cord was narrowed and pale. On cross section the gray matter was poorly

demarcated from the white matter. The fine vascular ramifications within the pia were obliterated. In a few of the cases, in which the compression was rapid, the spinal cord was extremely soft, even to the point of liquefaction, and the meningeal vessels were congested. This was probably the result of infarction and suggested that ischemia was a relatively important factor in acute and probably also in chronic compression of the spinal cord.

In microscopic sections of the spinal cord there was considerable variation from case to case. The usual findings were small irregularly shaped areas of fenestration occurring in the more superficial parts of the white matter and imparting a cribriform appearance. These vacuolated spaces ranged in size from 25 to 100 μ, and in many of them there was a round homogeneous body, representing a dilated axis cylinder. In more chronic lesions the axis cylinders had disappeared and one or several microglial phagocytes could be seen. Astrocytes were increased in number and size. Sometimes one or two small foci of ischemic necrosis were present and depending on the age of the lesion the tissue was poorly stained and structureless or was replaced by microglial phagocytes. In the acutely necrotic lesions the portion of the spinal cord below the involved segment was completely disorganized. All structures except possibly blood vessels, the connective tissue septa and pia had disappeared and if the lesion was more than a week or two old a pronounced microglial proliferation was present. Proliferation of astrocytes was a later event. Occasionally a thrombosed vein or artery was seen but these were not found with sufficient regularity to account for the deprivation of blood supply.

Infiltration and compression of spinal roots and ganglia occurred in some cases. In lymphosarcoma or lymphatic leukemia tumor cells insinuated themselves between fascicles of nerve fibers and along the perineurium. The exact mechanism of damage was not apparent because similar infiltrations by inflammatory cells, so frequent in a bacterial leptomeningitis, seldom damage nerve fibers. Compression may have been a factor especially when the sensory ganglia and nerves were implicated in the intervertebral foramens. Similarly small masses of tumor cells sometimes infiltrated the meninges. The infiltrating masses were at times so diffuse or so small as to escape detection on gross examination.

B. Clinical

In reviewing our cases and also the case reports in the literature it was striking how often the true nature of the disease escaped recognition until a surgical biopsy or an autopsy was performed. In part this is due to the rarity of lymphomas and especially those associated with neurological symptoms. Seldom does one neurological physician build up a sufficiently large clinical experience to become thoroughly familiar with all aspects of this problem. Another source of error has been the lack of careful neurological examination of patients suffering from lymphomatous diseases. Often these patients were on a medical ward, desperately sick, and were not available to the neurologist.

There are four outstanding clinical syndromes in lymphomatous diseases of the nervous system. The first and most frequently encountered one was that

caused by an acute or subactue compression of the spinal cord. The rapid evolution, in the period of a few days up to a few months, of a paraplegia with corresponding sensory loss and sphincter paralysis preceded or accompanied by pain in the back or by radicular pains should always suggest the possibility of a spinal epidural lesion of lymphomatous character. The differential diagnosis should include metastatic carcinoma and granuloma of pyogenic or tuberculous nature. Other rare types of malignant epidural growths may occur and offer diagnostic difficulty. It is well to remember that this neurological picture may precede involvement of other viscera. Paraplegia occurs with lymphosarcoma, Hodgkin's disease, either granuloma or sarcoma, reticulum cell sarcoma and plasmacytoma. In cases with complete spinal block the characteristic "loculation syndrome" of yellow fluid under low pressure, spontaneous clotting and very high protein are present. In partial block only slight to moderate elevation of protein and interference with jugular dynamics occurs. Pleocytosis occurs in a small percentage of cases; the cells in our cases were usually identified as lymphocytes but carefully stained smears were not examined. The X-ray picture does not usually distinguish the lymphomas from one another or from other tumors or tuberculosis. The X-ray appearance of multiple myeloma was quite characteristic but the other types of lymphoma usually produced poorly defined, irregularly shaped areas of rarefaction without evidence of bone proliferation. Areas of increased bone density were present in only a few of the more chronic cases. The intervertebral discs were not destroyed as they are in some cases of tuberculosis.

A second neurological symptom-complex is the successive implication of cranial nerves or rarely of the cerebral cortex. The cranial nerve palsies most frequently seen are trigeminal, abducens, facial, auditory and glossopharyngeal. A combination of headaches, drowsiness, convulsions, hemiplegia and hemianesthesia and aphasic disorders attest the damage of the cerebral cortex. Often local pain, swelling or infiltration of extracranial tissues indicates the presence of the tumor. As a rule well directed X-rays of the skull will show bone destruction. Plasmacytoma, reticulum cell sarcoma and lymphosarcoma exhibit this tendency to infiltrate the sphenoid, temporal or parietal bones. Lymphomatous lesions of the sphenoid bone must be distinguished from transitional cell carcinomas of the nasopharynx with extension to sphenoid bone and from chordomas.

The third clinical syndrome is that of meningeal invasion by lymphoma with or without cranial or spinal nerve implication or cerebral invasion. This condition was seldom recognized until other outspoken manifestations of the disease appeared. Usually complaints of headache, slight neck rigidity and rarely nausea and vomiting were the chief symptoms. Later, convulsions with hemiparesis, mental changes and any of several combinations of cranial nerve palsies were added. As a rule the pleocytosis in the cerebrospinal fluid, usually lymphocytes, occasionally immature, always led to consideration of infectious diseases, such as either virus, tuberculous, syphilitic or fungous meningitis or of epidural or brain abscess. When these conditions have been excluded by appropriate

tests or when lymphadenopathy, splenomegaly or other visceral involvement is evident, meningeal invasion by lymphoma becomes a probable diagnosis. This syndrome was most often produced by lymphosarcoma or lymphatic leukemia.

The fourth and least well recognized clinical condition is primary cerebral lymphoma. In middle-aged or elderly adults lymphoma must be considered with glioma (usually glioblastoma multiforme) and secondary carcinoma as possible causes of a rapidly developing brain tumor. In none of our cases was the correct diagnosis made prior to operation. The duration of symptoms before operation was weeks to a few months. Pronounced mental confusion, stupor or even coma without much papilledema or greatly elevated cerebrospinal fluid pressure were reminiscent of metastatic carcinoma or glioblastoma. The type of focal neurological signs varied with the location of the tumor. In a surprisingly high percentage of these cases (all three cases of Hodgkin's sarcoma and one of the three cases of reticulum cell sarcoma) there were a few lymphocytes, 10 to 50 per cubic mm., in the cerebrospinal fluid but unless the sediment of centrifugalized fluid, is "blocked" and cut in section in order to demonstrate tumor cells this information will probably be of little assistance in diagnosis because similar changes may be found in glioblastoma. Reticulum cell sarcoma and Hodgkin's sarcoma were the types of lymphoma which were primary in the brain. There were no proved instances of Hodgkin's granuloma and other forms of lymphoma originating in this organ. We have not observed brain metastases in Hodgkin's disease, reticulum cell sarcoma or multiple myeloma.

The best treatment of lymphomas of the nervous system can not be satisfactorily determined from our material. However, certain principles do seem apparent. In general whenever a spinal epidural tumor develops as a first event in an illness, laminectomy and surgical biopsy are indicated. All tumor tissue easily accessible should be removed and the spinal cord decompressed. This is expecially important in reticulum cell sarcoma of a vertebra because of its relatively good prognosis when properly treated. Roentgen therapy should follow the operation and be repeated whenever spinal symptoms recur. By these measures good recovery of neural function and quite long survivals have occasionally resulted. When spinal cord compression develops late in the course of Hodgkin's disease or other lymphomas the operative results are much less satisfactory. Death usually occurs within a few weeks whether or not operation is performed. Intensive x-radiation to the spine is probably preferable to surgical treatment. As with all spinal compressive syndromes good operative results are rarely achieved if spinal cord symptoms have developed rapidly and if paraplegia and sensory loss are complete. Roentgen therapy to the affected part of the neuraxis is the treatment of choice when infiltration of the meninges is present.

In Hodgkin's sarcoma and reticulum cell sarcoma of the brain craniotomy and surgical biopsy are indicated. Since these tumors are quite easily separated from the brain tissue and removed (no tumor was found at autopsy in two of our cases) they should be removed as completely as possible. Roentgen therapy should be given post-operatively. With proper surgical management better

results might be expected than with glioblastoma or solitary metastatic carcinoma.

SUMMARY

This communication contains a summary of the clinical and neuropathological findings of 19 cases of lymphoma involving the central nervous system. These cases were studied at the Mallory Institute of Pathology between the years 1930 to 1945 during which time 118 cases of lymphoma were autopsied. Seven additional cases with a surgical biopsy of a spinal epidural lymphoma and two cases from another hospital are included. Among these 28 cases are one of lymphosarcoma with spinal cord compression, three cases of lymphatic leukemia (one with a spontaneous cerebral hemorrhage, one with meningeal and cranial nerve infiltration and one with infiltration of the spinal ganglia and leptomeninges), one case of giant follicle lymphoma which had undergone transition to a reticulum cell sarcoma with meningeal and spinal nerve root involvement, one case of Hodgkin's granuloma with spinal cord compression, six cases of Hodgkin's sarcoma (one primary in brain, two questionably primary in brain and three in the spinal epidural space), eight cases of reticulum cell sarcoma (three primary in brain, one extending from cranial bone to the meninges and brain, one extending from cranial bone to dura, and three of spinal epidural space), and eight cases of plasmacytoma or multiple myeloma (one with meningeal infiltration, two with cranial nerve compression and five of spinal epidural space). Clinical and pathological summaries of 21 of these 28 cases are presented. The histogenetic classification of lymphomas which has been adopted at this laboratory is reviewed. The general pathological and clinical aspects of involvement of the central nervous system by lymphoma as deduced from our material are discussed in detail.

REFERENCES

1. Jackson, H., Jr., and Parker, F., Jr.: Reticulum Cell Sarcoma, Oxford University Series, Vol. IV, Chap. I-E, 67–93, Oxford University Press, New York, 1944.
2. Jackson, H., Jr., and Parker, F., Jr.: Giant Follicle Lymphoma and Lymphosarcoma, Oxford University Series, Vol. IV, Chap. I-E, 95–114, Oxford University Press, New York, 1944.
3. Jackson, H., Jr., and Parker, F., Jr.: Hodgkin's Disease, II. Pathology, New England J. Med. **231**: 35–44 (July 13) 1944.
4. Jackson, H., Jr., Parker, F., Jr., and Bethea, J. M.: Studies of Diseases of the Lymphoid and Myeloid Tissues. II. Plasmacytomata and Their Relationship to Multiple Myelomata, Am. J. Med. Sc. **181**: 169–180 (Feb.) 1931.
5. Virchow, R.: Die krankhaften Geschwulste, Berlin, A. Hirschwald, 1863, Vol. I., p. 543.
6. Murchison, C.: Case of "Lymphadenoma" of the Lymphatic System, Liver, Lungs, Heart and Dura Mater, Tr. Path. Soc. London **31**: 372–389, 1869–1870.
7. Mosler, F.: Zur Histologie der Leukamie, Virchows Arch. f. Path. Anat., **56**: 14, 1872.
8. Roncelli, F.: Sarkom des Nasenrachenraumes, 1 Fall, Jahresb. u. d. chir. Abt. d. Spit. in Basal, 1894, p. 19.

9. Guillain, Alajouanine and Périsson: Lymphosarcome extradural metastique ayant détermine une compression médullaire d'apparence primitive, d'évolution rapidement progressive; laminectomie; extirpation et radiothérapie; guérison, Bull et mém Soc. méd. d. hôp de Paris 49: 1057–1061, 1925.
10. Davison, C., ann Michaels, J. J.: Lymphosarcoma with Involvement of the Central Nervous System, Arch. Int. Med. 45: 908–925 (June), 1930.
11. Woltman, H. W.: Malignant Tumors of the Nasopharynx with Involvement of the Nervous System, Arch. Neurol & Psychiat. 8: 412–429 (Oct.) 1922.
12. Baker, G. S.: Lymphoblastoma Simulating Other Organic Diseases, Proc. Staff Meeting, Mayo Clinic 17: 588–592 (Dec.) 1942.
13. Verna, D. J.: Malignant lymphomas of the Spinal Epidural Space, S. Clin. of North America 24: 1228–1244 (Oct.) 1944.
14. Abbott, K. H., ann Adson, A. W.: Primary Intracranial Lymphosarcoma; report of 2 cases and review of the literature, Arch. Surg. 47: 147–159 (Aug.) 1943.
15. Trömner, E., ann Wohlwill, F.: Uber Erkrankungen des Nerven Systems, insbesondere der Hirnnerven bei Leukämie, Deutsche Ztschr. f. Nervenh. 100: 233–259, 1927.
16. Diamond, I. B.: Leukemic Changes in Brain; report of 14 cases, Arch Neurol. & Psychiat. 32: 118–142 (July), 1934.
17. Schwab, R. S., ann Weiss, S.: Neurologic Aspects of Leukemia, Am. J. Med. Sc. 189: 766–778 (June) 1935.
18. Leinler, F., ann Russell, W. O.: The Brain in Leukemia, Arch. Path. 40: 14–33 (July) 1945.
19. Brill, N. E., Baehr, G., ann Rosenthal, N.: Generalized Giant Follicle Hyperplasia of Lymph Nodes and Spleen, J. A. M. A. 84: 668–671 (Feb.) 1925.
20. Sugarbaker, E. D., and Craver, L. F.: Lymphosarcoma; a study of 196 cases with biopsy, J. A. M. A. 115: 17–23 and 112–117 (July) 1940.
21. Baehr, G., and Klemperer, P.: Giant Follicle Lymphoblastoma, New York State Jour. Med. 40: 7–11 (Jan.) 1940.
22. Browner, J., and de Veer, J. A.: Lymphomatoid Diseases Involving Spinal Epidural Space: pathologic and therapeutic considerations, Arch. Neurol. and Psychiat. 41: 328–347 (Feb.) 1939.
23. Mallory, T.: Cabot Case #32281, New England J. Med. 235: 62–65 (July) 1946.
24. Ginsberg, S.: Hodgkin's Disease with Predominent Localization in the Central Nervous System, Arch. Int. Med. 39: 571–595 (Apr.) 1927.
25. Eugénis, Cimon: Les Manifestations cérébro-médullaires de l'adénie éosinophilique prurigène, Thèse de Lyon, 1929.
26. Weil, A.: Spinal Cord Changes in lymphogranulomatosis, Arch, Neurol. & Psychiat. 26: 1009–1026 (Nov.) 1931.
27. Viets, H. R., ann Hunter, F. T.: Lymphoblastomatous Involvement of the Nervous System, Arch. Neurol. & Psychiat. 29: 1246–1262 (June) 1933.
28. Martin, H. E., ann Counville, C. B.: Hodgkin's Disease with Involvement of the Cranial Dura Mater, Bull. Los Angeles Neurol. Soc. 1: 145–148 (Dec.) 1936.
29. Von Haden, K. O.: Lymphogranuloma (Hodgkin's Disease) with Involvement of the Spinal Cord, Bull. Los Angeles Neurol. Soc. 20: 20–25 (Mar.) 1937.
30. Gray, R. C., Baker, A. B., Cottrell, L., and Koglano, S.: Hodgkin's Disease of the Central Nervous System, Internat. Clinics, Vol. IV, (New Series) 230–236 (Dec.) 1941.
31. Winkleman, N. W., ann Moore, M. J.: Lymphogranulomatosis (Hodgkin's Disease) of the Nervous System, Arch. Neurol. & Psychiat. 45: 304–318 (Feb.) 1941.
32. Jackson, H., Jr., and Parker, F., Jr.: Hodgkin's Disease. V. Involvement of Certain Other Organs, New England J. Med. 233: 369–376 (Sept.), 1945.
33. Von Hecker, H., and Fischer, W.: Zur Kenntnis der Lymphogranulomatose, Deutsche med. Wchnschr. 48: 482–484 (Apr.) 1922.

34. Sparling, H. J., Jr., and Adams, R. D.: Primary Hodgkin's Sarcoma of the Brain: Report of a Case, Arch. Path. **42**: 338–344 (Sept.) 1946.
35. del Rio Hortega, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932.
36. Ewing, J.: Endothelioma of Lymph Nodes, J. M. Research **28**: 1–40, 1913.
37. Roulet, F.: Das Primare Retothelsarcom der Lymphknoten, Virchows Arch. f. Path. Anat. **277**: 15–47, 1930.
38. Bailey, P.: Intracranial Sarcomatous Tumors of Leptomeningeal Origin, Arch. Surg. **18**: 1359–1402 (April) 1929.
39. Yuile, C. L.: Case of Primary Reticulum Cell Sarcoma of the Brain: Relation of Microglial Cells to Histiocytes, Arch. Path. **26**: 1036–1044 (Nov.) 1938.
40. Ferens, E.: Case of Primary Reticulo-Endothelioma of the Central Nervous System, Neurol. Polska, **21**: 387–402, 1938.
41. Hsü, Y. K.: Primary Intracranial Sarcomas, Arch. Neurol. & Psychiat. **43**: 901–924 (May) 1940.
42. Benedek, L. and Juba, A.: Microglioma, Gyógyászat **81**: 233–226, (April) 1941; Uber das Microgliom, Deutsche Ztschr. f. Nervenh **152**: 159–169, 1941.
43. Fried, B. M.: Sarcomatosis of the Brain, Arch. Neurol. & Psychiat. **15**: 205–217 (Feb.) 1926.
44. Mage, J., and Scherer, H. J.: Tumeur cérebral parvicellulaire se propegeant dans l'espace de Virchow-Robin (la question des sarcomes adventitiels, périvasculaire ou périthéliaux), J. belge de neurol. et de psychiat. **37**: 731–746, (Dec.) 1937.
45. Kinney, T. D., and Adams, R. D.: Reticulum Cell Sarcoma of the Brain, Arch. Neurol. & Psychiat. **50**: 552–564 (Nov.) 1943.
46. Klemme, R. M.: Plasma Cell Myelomas Causing Cord Compression; Report of 5 cases, South. Med. J., **26**: 692–696 (Aug.) 1933; Klemme, R. M. as cited by Verda (14).
48. Walgren, as cited by Geschicter and Copeland (50).
49. Venturi, as cited by Geschicter and Copeland (50).
47. Geschicter, C. F., and Copeland, M. M.: Tumors of Bone, New York, American Journal of Cancer, 1936.

FILARIASIS IN AMERICAN ARMED FORCES IN WORLD WAR II

WILLIAM B. WARTMAN, Lt. Col., M.C., A.U.S.*

From the Army Institute of Pathology, Washington 25, D. C.

CONTENTS

* Morrison Professor of Pathology, Northwestern University, Chicago, Illinois.

INTRODUCTION

During August and September of 1942 filariasis was encountered for the first time among American troops. The men, who were stationed in the Samoan and certain other islands of the South Pacific Ocean, presented a strange syndrome consisting of painful swelling of the genitalia accompanied by retrograde lymphangitis and lymphadenitis of one or more of the extremities. Biopsies of involved lymph nodes led to discovery of adult filarial worms, but microfilariae were regularly absent from the blood. It is now established that the worms were *Wuchereria bancrofti*, and that most probably they were the nonperiodic variety. As far as is known there were no infections with other species of *Wuchereria* although it is possible that infection with the periodic variety of *Wuchereria bancrofti* as well as with *Wuchereria malayi* may have occurred.

General information about filariasis in soldiers has been given by the Surgeon General (4). Pathologic material from all available sources was collected at the Army Institute of Pathology and is the basis of this report. The patients included soldiers, sailors and marines infected during the present war, and a few soldiers of the regular army who were infected before the present conflict mostly in Puerto Rico. For the purposes of this paper the clinical picture of filariasis has been drawn from recently published reports of infections in military and naval personnel rather than from the records of the Army Institute of Pathology because the clinical portions of these records were inadequate. It should be emphasized that this paper deals only with filariasis in our own troops, and not with the disease in natives who inhabited the same places where the troops were infected.

MATERIAL AND METHODS

In the preparation of the clinical description of filariasis all papers published during the years 1943 to 1946 inclusive which are listed in the Quarterly Cumulative Index have been consulted. Seventeen of these reports contained sufficient data for statistical analysis of the authors' findings, and have been used in the preparation of the tables in this paper. Pertinent facts were culled from the other articles and incorporated in the text.

The pathologic material comprised biopsy reports and fixed tissues from 64 cases which were contributed by Army medical officers whose cooperation has greatly aided this study. No autopsy material came to hand.

Most specimens were fixed in 10 per cent formalin and a few in Zenker's fluid. Paraffin sections were prepared from all tissues and stained with hematoxylin and eosin. In some instances sections were stained by the Masson and Mallory methods for connective tissue, the Verhoeff and Van Gieson methods for elastica and connective tissue, the Foot and Wilder methods for reticulin, and the Goodpasture and Ziehl-Neelsen methods for bacteria. In most instances only a few sections were studied, but in selected cases partial or complete serial sections were examined.

EPIDEMIOLOGY

Age, Sex, and Race Incidence

Most reports do not include sufficient data to permit accurate determination of age, but it seems likely that the majority of patients were young men 18 to 26 years old. Flynn's patients were on the average 21.8 years of age with extremes of 18 and 50 years. Wartman's patients fell into the 18 to 26 year old group. The average age of Leede and Josey's patients was 26.6 years. Other authors (24, 32, 17, 5) stated that their patients were young.

All the patients were men, but there was no information about race. Material at the Army Institute of Pathology included 48 whites, 7 negroes, 4 Puerto Ricans, and 2 Chinese.

Geographic Locations Where Infections Were Incurred

The great majority of patients with well established filariasis had been in the Samoan Islands and were in all likelihood infected there (Table I). For reasons of military security some authors said merely that their patients were from islands in the South Pacific Ocean, by which they probably meant the Samoan Islands. The number of cases from Wallis Island (French Samoa) was unusually high. Coggeshall reported that 4 per cent of his patients were infected in the Solomon Islands (Guadalcanal and Bougainville), while Haviland stated that 3 per cent of his patients were infected there. Other islands from which cases were reported included Aitutaki (Cook Islands), Bora Bora, Ellice Islands, Tongareva, Tonga-tabu and Woodlark Island (Trobriand Islands). It should be remembered that in some islands, from which only a few cases were reported,

the diagnosis was made on clinical grounds only, and was not verified by covery of the causative parasite.

There was a biopsy from one case at the Army Institute of Pathology fr a patient who had, as far as is known, never been in Samoa or the Solon Islands. He had been at Milne Bay, Papua for 1 year; at Hollandia, Du

TABLE I

Epidemiological Data

AUTHOR'S REFERENCE NUMBER	NUMBER OF CASES	PLACE OF INFECTION	LENGTH OF EXPOSURE	INCUBATION PERIOD
			months	*months*
14	251	Samoa		1- 9.5
5	46	South Pacific		3-21.5
24	251	South Pacific		3.5+
16	125	Samoa	2-22 Av. 7.4	1-15 Av. 7.6
32	120	Samoa		7-9
48	268	Samoa	2-11 Av. 9	3+
17	large number	South Pacific		
26	189	Samoa		Av. 9.5
21		South Pacific—Majority; Solomon Islands, 3%	1-18	1-19
18	172	Samoa	1-23 Av. 9	2-22 Av. 5
15	127	South Pacific		3-14
8	1200+	Samoa, 96%; Solomon Islands, 4%	1-27 Av. 12.5	9
43	737	Samoa; Solomon Islands, 3%	3-17 Av. 9	
23	62	Tonga-Tabu	12	
41	30	Samoa	13-30	14-20
19	145	Samoa	2-23 Av. 14	
30	100	Samoa	16.3	2-22 Av. 13.3
51	532	Tonga-Tabu	12	2-18
53	35	South Pacific	3-6	4-9
55	2288	South Pacific		1-12

New Guinea; and Leyte, Philippine Islands, for short periods of time. seems likely that he was infected in Papua.

Length of Time Spent in Endemic Areas

Available data are given in Table I, which shows that the average length time spent in endemic areas by patients who later developed filariasis w approximately 11 months. The shortest time was 1 month and the longe 30 months. It should be remembered that these data included cases in whic

the diagnosis was made upon clinical grounds only, as well as cases in which the clinical diagnosis was confirmed by finding *Wuchereria bancrofti*.

Incubation Period

By "incubation period" is meant the time which elapsed between landing in an endemic area and the onset of symptoms. Because the definition refers to the onset of symptoms and not necessarily to the appearance of objective physical signs, calculation of the incubation period was based largely on the statements of patients, which was, of course, a possible source of error. However, most authors agreed that the incubation period in most cases was from 5 to 18 months, although not-infrequently patients were evacuated to the United States before adequate time had elapsed to determine the longest probable incubation period (Table I). Burhans, Camp, Butt and Cragg, and Wartman reported cases in which symptoms appeared 3 months after the first possible exposure, and in which adult worms were recovered by biopsy. Dickson, Huntington and Eichold described a case in which adult worms were recovered 5½ months after the first possible exposure to filariasis.

The Relation of Season to Onset

Available evidence indicated that onset of symptoms was not related to the season of the year. Of 737 cases reported by Smith, 3 per cent occurred during the period from July to September, 37 per cent from October to December, 16 per cent from January to April, and 10 per cent from May to September (sic). In Glauser's series of 172 cases the lowest rate of onset was in October, November and December, and the highest from March through August. In his group "neither the time of acquisition of the disease nor the onset of symptoms was seasonal, but spread over the entire year." Of King's 268 patients the majority had their onset during the period January to September, 1943. Burhans, Camp, Butt and Cragg reported that all 49 of their cases began in the period September to December. Although these authors thought that this observation might indicate a seasonal onset of the disease, it now seems probable that it resulted from other causes.

Relation of Time of Day to Onset

Burhans, Camp, Butt and Cragg, and Saphir found that the onset was usually at night. According to Glauser, however, "the onset of symptoms may occur at any time of the day or night." He found a nocturnal onset in 47 patients and a diurnal onset in 76.

Mosquito Vectors

Byrd, St. Amant and Bromberg made an extensive study of mosquito vectors in the areas in Samoa where troops were infected. The only transmitter of importance was *Aedes scutellaria pseudoscutellaris* (Syn. *A. variegatus*). They also described the development of the parasite in mosquitoes.

Number of Patients infected

Coggeshall stated that about 38,300 Naval personnel were exposed to filariasis and that the filariasis registry showed a total of 10,421 diagnosed cases in the Marine Corps and United States Navy as of December 1, 1945. Statistics were not available for the Army.

COURSE OF FILARIASIS IN AMERICAN ARMED FORCES

The clinical course of filariasis in our armed forces may be conveniently divided into 3 parts: (1) onset of disease; (2) physical signs in the early stages; and (3) physical signs in patients who were evacuated to the United States after the disease was well established or had subsided.

TABLE II

Onset of Symptoms

Results are either expressed in percentages or graded 0 none, + few, ++ many, +++ most.

	AUTHOR'S REFERENCE NUMBER																
	5	24	16	32	27	17	26	21	18	15	43	30	19	41	51	53	55
Genitalia	+++	72	50	+++	56	+++	97	33	53	75	11	61	+		47	+++	33
Arm	+++	22	38	+++	38	+++	61	30	24	++	75	26		30	16	+++	31
Leg	++	4	5	++	4		23	9	40	++	10			30		+++	9
Multiple sites					2	++					1			40	34		
Abdominal pain		++			1				1		+		+				
Pleurisy		++															
Pectoral swelling											1						
Neck pain and swelling					1										3		3
Headache		++					2	2								0	
Nausea		++		+						++		35	+			0	
Malaise		++					4		+++	+++	+++	42	+		++	0	
Backache							1		1	++		+					
Fever	+	+		+	1	+	1		20	0	0	+	+	0	++	3	

Onset of Disease

Table II gives the available facts about the way in which the disease began. It is obvious that symptoms referable to the genitalia,[1] arms and legs were complained of most frequently in that order. Of a total of 2124 patients (24, 16, 27, 43, 23, 30, 19, 41, 51) the first symptoms occurred in the genitalia in 899 (42 per cent), the arms in 517 (25 per cent), and legs in 234 (11 per cent). Other authors (14, 5, 17, 15), although not giving actual figures, confirmed these results. The data of Flynn and of Smith showed that symptoms referable to the genitalia occurred with equal frequency on the right side and the left side and bilaterally. Of 155 patients the left side was affected in 54, the right side in 50 and both sides in 51. The same authors reported that of 249 patients the left arm was involved in 64, the right in 100, and both arms in 85; the left leg in 28, the right leg in 31, and both legs in 145 of 204 patients.

[1] For convenience the words "genitalia" and "genital" will include the scrotum, testis and its coverings, epididymis and spermatic cord, but not the penis which was not attacked.

Simultaneous symptoms in the genitalia and extremities were noted in 317 of 1801 patients (18 per cent) (24, 27, 43, 23, 30, 41, 51). The arm and leg were equally involved.

The onset of symptoms which occurred infrequently is listed in Table II.

Genital Symptoms. These consisted principally of swelling and pain of the scrotal contents, and of pain in the groin (Table II). King found swelling in the scrotal region in 88.2 per cent of his patients, and Englehorn and Wellman noted that dense swelling of the testicle to twice its normal size was common. Pain in the scrotum and testis was very common and was usually mild, but occasionally it was severe (15). Patients frequently complained of soreness and tenderness of the testes. In King's series 82 per cent of the patients complained of pain in the scrotum or testis. Leede and Josey stated that the earliest symptom of filariasis was usually pain in the scrotum accompanied by a feeling of weight and a dull aching sensation in the testicle and cord. The patients of Hodge, Denhoff and Vanderveer complained most commonly of testicular pain which either radiated up the spermatic cord or started in the lower quadrant of the abdomen, and radiated down the spermatic cord to the testicle. Saphir observed that as time passed any mild exertion such as a brisk walk might cause testicular pain. Eventually the attacks became periodic, so that either with or without exertion symptoms recurred. Such attacks lasted a few hours to several days, followed by free intervals of days or weeks. Nocturnal attacks were frequent and even in quiet periods testicular pain might come on nightly. Rifkin and Thompson found that in many patients the onset of disease was an acute epididymofuniculitis.

Pain in the groin has been common in most reports, but has shown some variation. For instance, King found it in only 10 per cent of his patients, all of whom were infected in Wallis Island. Smith found it commonly in Marines infected in British and American Samoa, and uncommonly in sailors who were infected in Wallis Island and Samoa. Burhans, Camp, Butt and Cragg described the pain as sharp and drawing.

"Lumps in the groin" have been described (5) as well as suprapubic pain (15).

No patients had complaints referable to the penis.

Symptoms in the Upper Extremities. These consisted principally of swelling and pain in the affected part (Table II). An early symptom was numbness or weakness, the affected part feeling as though it was "falling asleep." This might be followed by aching and pain which usually started in the axilla and sometimes led to discovery by the patients of enlarged axillary lymph nodes (53). Pain was usually not severe and was often accompanied by stiffness (27). Many patients complained of aching and a sensation of heaviness in the arms (43). Transient redness, usually in the form of broad streaks, was another symptom, and was often accompanied by painful swelling. Pruritus, wheals, and tender fugitive swellings also occurred.

The part most frequently attacked was the medial surface of the forearm (27) although in some patients the pain was diffuse (30). In most patients whom Smith saw, "a firm swelling of the medial side of the forearm and the

were cardinal signs. The entire cord from the internal inguinal ring to its junction with the epididymis might be affected, and frequently the epididymis itself was involved. Sometimes there was only slight thickening of one side as compared with the other, but at other times the cord was enlarged from two to five times its normal size (15). The swollen cord was usually rubbery in consistency and sometimes nodular (27, 53). The pain varied from slight discomfiture to exquisite pain, similar to that resulting from a blow to the scrotum. As a rule pain and tenderness were more marked in the genitalia than the extremities. Marked tenderness over the internal inguinal ring and swelling of the cord where it emerged from the external ring were frequently detected early in the course of disease. According to Englehorn and Wellman, pain, tenderness, and swelling appeared in the scrotal contents and spermatic cord about two weeks after the earliest non-specific symptoms, and the swelling subsided in a few days. In some instances the lesions subsided completely after the acute attack, but in others thickening and nodularity of the cord persisted indefinitely. According to Leede and Josey funiculitis was one of the most permanent of all physical findings and once it occurred residua ensued. They also observed soft, dilated, easily movable veins in chronic filarial funiculitis or an inseparable thickening of all structures of the spermatic cord and pointed out that these findings may be misinterpreted as due to ordinary varicocele. Fogel and Huntington emphasized that swelling and edema of the spermatic cord were the earliest clinical signs of filariasis. The funiculitis was descending or retrograde and had its counterpart in the visible lymphangitis of an extremity. They were able to follow almost at hourly intervals the clinical development of the early stages of the lesions in three hospital corpsmen. The onset consisted of lower abdominal pain at which time the spermatic cords were normal to palpation. "Within 12 hours there was palpable swelling high up in the inguinal canal. The examining finger could be inserted through the external inguinal ring without causing much discomfort to the patient. As the hours passed the progress of the swelling could be palpated as it moved down the cord. Within 24 hours that part of the cord lying within the inguinal canal was greatly swollen and tender. It was difficult to pass the palpating finger through the external ring because of the swelling and tenderness of the cord. In the succeeding 24 hours a scrotal mass was visible and palpable." Such observations leave little doubt that the acute funiculitis was in reality acute filarial lymphangitis of the spermatic cord and was identical with the lymphangitis observed in arms and legs.

Epididymitis: The incidence of epididymitis varied in different series. King encountered acute epididymitis in 93 per cent and Hodge, Denhoff and Vanderveer in 76 per cent of patients, whereas Englehorn and Wellman, and Smith found it in only 17 per cent of theirs. Saphir reported 1 case among 35 patients. Behm and Hayman described an enlarged epididymis or testicle in 14 per cent of their filariasis patients and in 2 per cent of patients once suspected of having the disease, but in whom the diagnosis was later discarded. Other authors (14, 5, 24, 19) stated that it was common in their patients. According to

Fogel and Huntington epididymitis was present in some degree whenever the spermatic cord was attacked. Hodge, Denhoff and Vanderveer reported that it occurred slightly more often on the right side than on the left and was bilateral in about 25 per cent of cases. Goodman, Weinberger, Lippincott, Marble and Wright observed epididymitis most commonly on the left side. Usually the epididymis was enlarged, smooth, and soft. Tenderness was present, but was usually surprisingly slight. According to King, the globus major of the epididymis was most frequently involved and the body and globus minor only infrequently. In most instances the lesion subsided completely, but in some cases thickening and palpable nodules remained (12 per cent according to King). Fogel and Huntington stated that "in chronic epididymitis the epididymis is small and fibrotic." They attached considerable significance to the presence of a small, shot-like lymph node located where the vas deferens became distinctly palpable from the epididymis. This small sentinel node persisted for many months, but was absent in some cases.

According to Englehorn and Wellman the first physical finding was often acute epididymitis which appeared before the cord was involved and subsided in some cases with the onset of funiculitis.

Orchitis: Acute orchitis occurred in from 14 to 54 per cent of reported cases. Flynn observed it approximately equally on the left and right sides, but others (15, 19) found it more commonly on the left side. Burhans, Camp, Butt and Cragg thought that it was rarely bilateral. Flynn found bilateral lesions in 5 per cent of his patients. Symptoms consisted of pain, swelling, and tenderness. Testicular pain was a very common complaint and often radiated up the spermatic cord. In other cases it appeared first in the lower quadrant of the abdomen and radiated down the spermatic cord to the testicle (23). Although the pain and tenderness of the testes were more marked than in the lymphangitis of extremities, nevertheless, they were usually milder than would have been expected.

Fogel and Huntington considered that "a boggy edematous consistency of the testis was one of the most characteristic and persistent findings." They also noted that in some instances a scrotal mass would suddenly develop which did not transmit light. Aspiration of eight such cases yielded a small amount of fluid similar to that obtained from ordinary hydrocele. Most authors mentioned that there was commonly a small collection of fluid in the tunica during attacks of acute orchitis. Engelhorn and Wellman noted that pain often disappeared when scrotal swelling became maximal.

Inflammation of Scrotal Skin: Edema of scrotal skin was common (14,23, 5). King observed edema and erythema in 18.5 per cent of his cases and noted that it usually subsided very quickly. He described one case in which the "scrotal inflammation extended upwards as a streak of lymphangitis ending at the umbilicus." Goodman, Weinberger, Lippincott, Marble and Wright found scrotal edema in 7 to 12 per cent of their cases and Leede and Josey in 7 per cent. Fogel and Huntington also observed edema of the scrotum and found that when it was present it was always on the side where funiculitis

existed. There was, however, no relation between the degree of scrotal edema and the degree of swelling of the cord, nor were the regional lymph nodes always enlarged. Swelling usually occurred in the most dependent portion of the scrotum and the skin pitted on pressure, the pit marks disappearing within a short time. In mild cases the skin was red, but in severe cases it was pale. The cremasteric reflex was sluggish.

Lymph Scrotum: Behm and Hayman reported 1 patient who was separated from the service because of lymph scrotum. No other cases were reported.

Hydrocele: Small accumulations of fluid in the tunica vaginalis were a common accompaniment of acute orchitis and epididymitis, and occasionally large hydroceles were present. Small hydroceles were found in 10 per cent of King's patients. None of these required aspiration and all subsided before the patients were discharged from the hospital which was on the average 15 days. King noted that early filarial hydrocele in the absence of other findings might be impossible to distinguish from other inflammatory hydroceles. Fogel and Huntington aspirated 18 cases of hydrocele and obtained 10 to 50 cc. of fluid from each one. The fluid was amber and contained lymphocytes and in some instances numerous eosinophils. There were no flocculi. Microfilariae were not found. In 11 of these 18 cases the fluid reaccumulated rapidly, and the authors thought that the course was longer in cases in which aspiration was done than in those in which it was omitted. In a number of instances a persistent scrotal mass, which usually transmitted light, developed following several episodes of transient swelling, and disappeared on bed rest.

Many of Johnson's patients had accumulations of fluid which usually resulted in swelling no greater than a "large orange." Saphir reported hydrocele in 9 per cent of his patients. Goodman, Weinberger, Lippincott, Marble and Wright observed hydrocele, which was usually transient, in rare instances. Englehorn and Wellman did not encounter hydrocele, and Smith found it so seldom that he disregarded it.

Varicocele: Varicocele was reported by Fogel and Huntington; Englehorn and Wellman; Smith; and Saphir (29 per cent). The former authors found it commonly and stated that in a considerable number of cases the varices appeared for the first time during and after an attack of acute funiculitis. They believed that filarial funiculitis could "cause either the appearance of lymphatic varices or the exacerbation of venous varices." They noted that filarial varicocele, like ordinary venous varicocele, occurred most commonly on the left side which they attributed to mechanical factors.

Englehorn and Wellman stated "varicoceles usually lasting only a week or two developed in some patients with funiculitis. In some instances there was an exacerbation of a chronic varicocele. No diagnostic weight was given to this particular development because of its frequent occurrence in other circumstances."

Smith wrote, "the relationship of filariasis as an etiologic factor in the production of varicocele is not fully determined."

Lymphangitis. Most authors agree that acute lymphangitis was a char-

acteristic feature of acute filariasis. King found it in 51 per cent of his patients and Rifkin and Thompson in 60 per cent of theirs. Others (14, 5, 24, 32, 17, 26, 18, 51) reported that it was common. Flynn stated that he observed only two cases of the extremities in which "the diagnosis of lymphangitis could not be surmised." Englehorn and Wellman; Leede and Josey; Goodman, Weinberger, Lippincott, Marble and Wright; Smith; and Hodge, Denhoff and Vanderveer, reported a low incidence of lymphangitis. Smith, Leede and Josey, and Goodman, Weinberger, Lippincott, Marble and Wright, observed their patients after they had been away from the endemic area for 3 to 5 months which may explain why lymphangitis was not common. The cases of Englehorn and Wellman, and Hodge, Denhoff and Vanderveer, on the other hand, were observed during the initial attack in endemic areas, and there was no apparent explanation for the low incidence of lymphangitis. Saphir did not see retrograde lymphangitis among 35 patients in a "station hospital in the

TABLE IV

Lymphangitis

Legends are the same as in Table II

	AUTHOR'S REFERENCE NUMBER																	
	14	5	24	16	32	27	17	26	21	18	15	8	43	23	41	19	30	53
Eyebrow						0.4												
Neck			++			1	+			1		2						
Arm	22	+++	22		++	48	+	49-66	7			30	1	19	30			
Groin		++				0.8												
Leg	4		4		++	7	+	13-31					0.1	3	3			
Buttocks						0.8												
Abdomen						0.4												
Total	26	+++		2	+++	51	+++		7	1	6	32	1	23	60	4	4	0

South Pacific Forward Area" although they had other symptoms suggestive of early filariasis.

Lymphangitis occurred in many situations as shown in Table IV, but no matter where it occurred there were certain common characteristics. Chief of these was a tendency to spread in a retrograde direction. Most authors stated that the inflammation frequently started in a lymph node and only later attacked lymph vessels, but occasionally lymphangitis was present without lymphadenitis. A definite red streak with edema appeared proximally. Some authors described local heat (27) while others said it was absent (51). The affected lymphatic was palpable and generally only a single vessel was involved. Resolution began proximally and also showed retrograde regression. The lymph nodes draining the affected part were enlarged and tender. There was very little febrile reaction and the lesion was not associated with bacterial infection. Pain was almost always described as being less intense than would be expected from the severity of physical signs. King mentioned that "in a few instances, after the acute erythema had subsided, ecchymotic discoloration

of the skin was present, usually overlying a subcutaneous cord-like structure." There was neither desquamation of skin, vesicle or bullous formation, nor suppuration of satellite nodes. Attacks usually lasted a few days and the lesions often began to fade within 24 hours. Recurrences were common. During remission the affected part was apparently normal.

Upper Extremities: King's description of filarial lymphangitis of the arm is representative and will be quoted in full: "The lymphangitis of the arm occurred most commonly along a course overlying the brachial vessels or on the volar surface of the forearm. It took three forms: A red streak of varying length often with an underlying firm irregular cord, most common in the upper arm; patches of subcutaneous edema and overlying redness, irregular in outline and of varying size and most common on the anterior surface of the forearm; and diffuse edema and erythema of the upper arm or forearm. With the erythema there was increased local heat. Tenderness was mild or moderate, rarely severe. The streaks were often multiple and in one case there was a graphic anatomical demonstration of all the superficial lymphatics of both the upper and the lower arm outlined by the inflammatory reaction. The irregular cords, formed along the lymphatics, persisted after the acute inflammation subsided, but over a period of a few days, tended to disappear. Residually there were at times poorly-defined areas of subcutaneous induration or nodules which felt like lymph nodes. In other instances there were only patches of subcutaneous edema, of a peculiar 'blubbery' consistency, with erythema or tenderness, and which tended to persist for two or three weeks."

Patients frequently noted painful swollen red areas in the extremities which later involved adjacent lymph nodes and were followed by retrograde lymphangitis (32). Many observers noted that the disease usually began in a lymph node and only later extended to lymph vessels rather than the other way around. The lymphangitis was usually well defined, the area being dull red, tense, swollen and cord-like. The red streaks were usually shorter, broader, paler, and more diffuse than in bacterial lymphangitis and were not tender (18). The lymphangitis frequently proceeded from the axilla down the arm toward the elbow, or from the epitrochlear or antecubital region down the forearm to the wrist and hand (51).

Johnson described "quiescent cases" in which the forearm was often slightly indurated in the cubital fossa and upper third just to the ulnar side of the midline. Smith only found a firm swelling usually on the medial and volar sides of the forearm in most of his patients. Burhans, Camp, Butt and Cragg observed occasional diffuse thickening of subcutaneous tissues.

Burhans, Camp, Butt and Cragg described cases in which small tender knots or elongated lumps developed along vessel paths or at the edges of muscles. Similar spindle shaped swellings, about 6 to 10 cm. long and 2 to 3 cm. wide, were seen by Glauser on the ulnar and volar aspects of the forearm.

Residual findings such as induration along lymphatic trunks with nodular thickenings have been described (19).

Lower Extremities: Lymphangitis of the legs was relatively uncommon varying from 3 per cent (23) to 31 per cent (26). The lymphangitis was usually

along the medial surface of the thigh and definite streaks were unusual. It often progressed from the inguinal region either down the inner aspect of the thigh, or characteristically around the lateral aspect of the thigh, above the greater trochanter, to the gluteal region (51). Patches of swelling in the popliteal area, the calf, or about the ankle were observed (27). Smith described one case in which he palpated a "cord-like fullness in the thigh." He also found spindle shaped swellings with occasional lymphangitis over the calf of the leg. Johnson noted that patients with demonstrable lesions elsewhere sometimes complained of pain in the popliteal space and the medial aspect of the thigh. An occasional patient presented slight swelling of the ankles without other signs of lymphangitis.

Neck: King observed three patients with transient lymphangitis on the side of the neck. Glauser described two patients who complained of neck pain. Coggeshall reported that 2 per cent of his patients ("a large series") showed lymphangitis of the neck, all of them accompanied by lymphadenitis. Fogel and Huntington stated that one should look for acute lymphangitis in the neck as well as in other situations.

Eyebrows: King described one case of lymphangitis over an eyebrow.

Deep Lymph Vessels: Involvement of deep lymph vessels of abdomen and extremities was stressed by Hodge, Denhoff and Vanderveer. "In many patients exposed to filariasis, one must be constantly on the alert for manifestations suggesting deep lymphatic involvement. By and large we have felt that the diagnosis of involvement of the retroperitoneal lymph nodes has been easier to recognize clinically than involvement of the deep lymphatics of the extremities. Pain in the flank or the abdomen, with radiation to the genitalia or the thigh is the principal complaint. Examination reveals tenderness of the abdomen on the affected side both anteriorly and posteriorly. In such cases it is necessary to rule out renal or ureteral disease which these findings may simulate. The only complaint in patients thought to have involvement of the deep lymphatics of the extremities is pain, with peripheral radiation. Slight swelling may or may not be present. The differential diagnosis includes skeletal, muscular, and neurologic conditions. These are extremely difficult to rule out and in only a few instances have we felt that this has been done to our entire satisfaction."

Chronic Lymphangitis: Behm and Hayman reported 5 cases of chronic lymphangitis among 532 men 2 years after they were removed from Tonga-tabu.

Recurrent Lymphangitis: Recurrences were so common as to be characteristic of early filariasis. They will be discussed more fully in a later section of the paper (Relapses). However, attention should be directed at this point to a patient of Behm and Hayman who was discharged from the service because of persistent recurrences of lymphangitis.

Miscellaneous: Burhans, Camp, Butt and Cragg, and King described lymphangitis in the groin. In two of King's cases the streak of lymphangitis started in the groin and extended laterally about the hip nearly to the intergluteal fold. In another of King's cases a streak of lymphangitis extended from the scrotum to the umbilicus.

Lymphedema. Behm and Hayman reported one patient who had to be separated from the service because of persistent lymphedema of both legs. Coggeshall stated that lymphedema was the least frequent physical sign. He observed it in various locations, frequently as a cold puffiness 2 to 6 inches in diameter and raised ½ to 1 inch. It occurred around the cubital fossae, over the scapular and deltoid regions and occasionally about the eyes. It seems likely that the lymphedema of these authors and the transient swellings of others were identical.

Lymphadenitis. Swollen, tender, discrete lymph nodes without attachment to the skin or suppuration were characteristic of filariasis, and were described by all authors. The incidence varied. For example, King found enlargement of lymph nodes in 85 per cent of his patients, but on the other hand Englehorn

TABLE V

Lymphadenitis

Legends are the same as in Table II

	AUTHOR'S REFERENCE NUMBER																	
	14	5	24	16	32	27	17	26	21	18	15	43	23	19	30	51	53	55
Cervical		++	++			0.4	+					33				2		
Supraclavicular						0.7											3	
Axillary			+++	62		36	+	++			++	70		+	+++	49	100	1.1
Epitrochlear	+++	++	+++	49		53	+++	++		+	++	38		+	+++	24	31	0.4
Inguinal	+++	+++		97		35	+++	+++		+++		89		+++		76	100	2.4
Femoral				93		39						72				51	100	1.7
Popliteal																	9	
Pectoral																	9	
Generalized		++								+		1					++	
Total	+++	+++	+++	97	+++	85	+++	+++	31	+++	7	69	+++	85	92		100	

and Wellman found it in only 7 per cent. Smith stated that lymphadenitis was the only physical sign in 69 per cent of his patients.

Most medical officers found that it was difficult to judge the significance of palpable lymph nodes when the enlargement was slight. This was especially true in the inguinal region, and Fogel and Huntington pointed out that evaluation of inguinal lymphadenopathy was rendered difficult by the high incidence of epidermophytosis of the foot in the tropics.

Many authors have emphasized that filariasis often started in a lymph node and then spread to lymphatic vessels, but King also found lymphangitis without lymphadenitis in 15 of his cases. Johnson observed that lymphadenitis, in contrast to lymphangitis, was not always retrograde, for enlarged axillary nodes were sometimes present when the epitrochlear nodes could not be palpated. Epitrochlear lymph nodes, however, were particularly prone to attack (14, 5, 24, 27, 17, 43, 30, 41, 19, 23, 51, 53). Enlargement of cervical, supraclavicular, axillary, epitrochlear, inguinal, and femoral lymph nodes was reported by most authors. Generalized lymphadenopathy was described by King (4 cases), by

Burhans, Camp, Butt and Cragg, by Glauser, by Smith (96 cases), by Leede and Josey and by Saphir (35 cases).

In the epitrochlear region the nodes were firm, discrete, and usually single, although occasionally small clusters were present. In some cases there was a chain of nodes stretching from the epitrochlear region nearly half way to the axilla. Occasionally isolated nodes occurred in the antecubital fossa or the midhumeral region along the course of the brachial vein. Enlargement was usually moderate, but occasionally the nodes measured 4 to 5 cm.

Inguinal and femoral nodes were usually moderately enlarged and the enlargement was more commonly on the left than the right side (19) but was often bilateral. When the enlargement was marked, tenderness was also present but usually subsided quickly. Inguinal adenitis, although present in many patients who had genital lesions, was sometimes absent in those who had severe genital involvement, and was commonly most marked on the side opposite from the genital involvement (17). The nodes were typically elongated and spindle shaped (17, 18).

Enlarged lymph nodes could sometimes be palpated in various odd places, especially in the intercostal region, the popliteal spaces, in the back, wrist, tip of the ilium, midarm, and in the region of the teres and serratus muscles (26, 41, 30, 43). They were not always symmetrical, and the asymmetry of the lymph node enlargement was helpful in diagnosis. Pectoral lymphadenopathy was described in 3 cases by Saphir. The enlarged nodes extended in a chain from the axilla along the margin of the pectoral muscle to the nipple. In one case swelling and tenderness were so marked that an erroneous diagnosis of acute mastitis was made. Involvement of retroperitoneal lymph nodes was thought to give rise to acute and chronic gastro-intestinal symptoms (43). Smith found that the satellite node of filariasis was smaller and firmer than that arising from pyogenic lymphangitis of similar degree, and that it did not enlarge regularly with extension of the lymphangitis.

Enlargement of all nodes tended to persist. In many patients who were observed over long periods of time the adenopathy remained unchanged, and in a few became more extensive. Varicose nodes have not been reported.

Hodge, Denhoff and Vanderveer have suggested that the clinical manifestations of filariasis depended on the situation of the particular lymph node in which the adult filaria responsible for the reaction was located. Thus, if the adult filaria was located in pelvic or peri-aortic lymph nodes, genital manifestations resulted. If the worm was in a lymph node draining the superficial lymphatics of an extremity, this part would be affected. Similarly if the lymph node affected was one draining a deep lymph vessel where the reaction could not be seen or felt, the diagnosis might not be apparent.

Hypersensitivity. Transient swellings and urticaria have been described in many patients. They were observed only in the acute stages of filariasis and usually only in endemic areas. Although the hypersensitive nature of these signs is not proved, it is convenient to consider them as such for purposes of discussion.

Transient or Fugitive Swellings: These have been described in the arms (32, 15), legs (32, 15), wrists (27), hands (15), feet (14), torso (32), eyelids (5, 15), and forehead (17). According to Burhans, Camp, Butt and Cragg they developed along the path of lymphatic vessels or at the edges of muscles, and were sometimes accompanied by diffuse thickening of subcutaneous tissues. Fogel and Huntington observed them in areolar tissue. The swellings were usually raised, slightly to moderately tender, red, and sometimes resembled erythema multiforme. Usually they lasted from a few days to two weeks and when they disappeared left little or no residua. Some measured 3 to 6 inches in diameter while others were much smaller. Suppuration did not occur. Often they were accompanied by urticaria. Some authors considered these lesions counterparts of the Calabar swellings of loiasis. Michael studied biopsies of fugitive swellings from 3 patients and found "typical allergic phenomena. The tissue appeared edematous with vascular engorgement and some perivascular round cell infiltration. The supporting structures were edematous and there were numerous eosinophilic cells present. No worms or microfilariae were seen."

Urticaria: King found that the onset of filariasis was manifested occasionally by giant urticaria. Urticaria occurred during the course of filariasis in all parts of the body either as a wide-spread or an isolated phenomenon (5, 17, 15).

Skin Rash: Smith observed a macular erythematous rash in 3 patients with filariasis.

Conjunctivitis. Conjunctivitis was seen occasionally by Michael, and commonly by Fogel and Huntington, who stated that it was serous in nature and accompanied by photophobia. No further information was given about this manifestation of filariasis.

Filarial Fever. Filarial fever was noted in the protocols of the Army Institute of Pathology in one Chinese and one Puerto Rican patient, both of whom had long-standing infections. It was not observed in patients with early infections.

Filarial Abscess. Huntington, Fogel, Eichold and Dickson stated that filarial abscess was most unusual in their patients. King did not observe it. Glauser reported two instances in which "suppurating glands developed on the outer surface of the arm along the edge of the biceps muscle and had to be incised. Free pus was obtained. The third patient gave a history of a suppurating inguinal gland while he was in Australia." According to Englehorn and Wellman "abscesses considered to be associated with filariasis developed in two soldiers following cellulitis of the elbow region. On incision the abscesses were deep and had many pockets which had to be broken up in order to effect complete drainage. The pus obtained was thin, greenish in color, and showed no organisms on direct microscopic examination. These lesions grossly resembled the abscesses which were observed among natives."

Mental Manifestations. Mental manifestations consisting principally of depression, irritability, nervousness, anxiety, worry and fear have been described (14, 18, 15, 9, 43, 42, 19, 51, 54, 55). Nearly all these patients had seen numerous cases of elephantiasis among natives. They were worried lest they develop similar disfiguring and incapacitating lesions and anxious about loss of

potency or fertility. Reassurance was effective in relieving the mental symptoms in many instances, but in some patients even persistent reassurance failed, chiefly among those with a past history of psychoneurotic behavior. On the other hand, Hodge, Denhoff and Vanderveer did not observe serious psychosomatic manifestations in their patients.

Sexual Function. There was no evidence that impairment of either libidinous or procreative sexual functions resulted from filariasis in the armed forces. Zeligs wrote that 45 (18 per cent) of the wives of 249 married Marines, who had a history or signs of filariasis, were pregnant or had given birth to healthy

TABLE VI

Miscellaneous Clinical Findings

Legends are the same as in Table II.

	AUTHOR'S REFERENCE NUMBER																	
	14	5	24	16	32	27	17	18	15	8	43	23	19	30	51	53	54	55
Fugitive swellings	+	++	++		++		+	+	+					7				
Urticaria		++	++			+	+++		+									
Conjunctivitis					+		++											
Abscess			+					1	2									
Disturbance of sexual function							0	0		0	+				0		0	0
Mental depression, etc.	+++							+	+++	+++	++		+++		+++		+++	+++
Duration of attacks (days)		3–4	*	3–5	2–5	7–14	*		1–7	*						*		*
Relapses		+++	+++	+++	+++	+++	+++		+++	+++					+++	+++		+++

* Several.

children. Coggeshall reported that 107 of 504 marriages among Marines with a diagnosis of filariasis resulted in pregnancy within 6 months. The incidence of sexual disturbances of psychogenic origin, such as psychic impotence and fear of sterility was 2.8 per cent (27 of 906 patients), which was about the expected rate for any group of individuals. Behm and Hayman reported 33 patients who believed their sexual potency had been impaired by filariasis. Glauser reported that among 13 patients who married 5 pregnancies resulted within one year. Coggeshall also reported that many of his patients had married and were raising families. Smith stated that many of his patients complained of loss of libido, but most authors mentioned no signs or symptoms indicating a loss of sexual function.

Duration of Attacks. Individual attacks were relatively brief lasting

3 to 5 days. In some patients the attacks were shorter and in a few they were longer, lasting for as long as 2 weeks or rarely a month (51). All observers were agreed that manifestations of filariasis were surprisingly transient and signs which were definite at one examination might be quite different a few hours later.

Relapses. Frequent relapses, occurring at intervals of a few weeks to several months, constituted one of the most characteristic features of early filariasis in the armed forces. In most patients the relapses tended to become less frequent and less severe with the passage of time, but during the first year or 18 months of disease this was not always true, and the relapses often increased in severity and frequency. Patients in relapse have been observed as long as two years after their initial attack (9). Hard exercise, fatigue, and hot climate were reported to bring on attacks or increase the severity of symptoms. Behm and Hayman estimated that the number of attacks varied from 1 to 12 as follows:

No. of attacks	*Men*
1	139
2	99
3	76
4	53
5	21
6	10
7	1
8	2
10	3
12	3
13	1

The question of the outcome of the disease will be taken up in the next section.

Follow-up Studies. Several authors (26, 43, 19, 30, 51, 54) have compared the early manifestations of filariasis with those which occurred later after the patients had been evacuated to the United States. Johnson described a marked improvement in patients after they had been in the United States for more than 107 days. Smith observed that filariasis became much milder after patients were evacuated to New Caledonia from Wallis Island and Samoa. Goodman, Weinberger, Lippincott, Marble and Wright compared the observations recorded during the first attack of filariasis overseas with those made at Harmon General Hospital (Texas) 2½ to 5 months afterward. Of 145 patients 135 (93 per cent) had lymphadenopathy during the first attack and 123 (85 per cent) subsequently in the United States. Lymphangitis occurred in 19 (13 per cent) overseas and in 6 (4 per cent) in the United States. Scrotal edema was found in 18 (12 per cent) overseas and 10 (7 per cent) in the United States. The incidence of funiculitis was 119 (83 per cent) overseas and 127 (88 per cent) in the United States. Orchitis occurred in 38 (26 per cent) overseas and in 8 (6 per cent) in the United States. During the period of observation at Harmon General Hospital physical signs and symptoms gradually disappeared. Lymph nodes decreased in size, and tenderness and thickening of the spermatic cord tended to disappear. Gradual exercise usually was not harmful, but did apparently precipitate attacks

of lymphangitis in 3 patients. The severity of these attacks, however, was not as great as earlier ones. Leede and Josey reported similar observations in their cases.

Coggeshall had the opportunity of observing 2595 Marines and sailors with filariasis at Klamath Falls, Oregon, for a period of 17 months. Only 22 per cent ever showed objective signs if the presence of shotty lymph nodes was ignored and only 18 men (0.07 per cent) had to be hospitalized for recurrences. The majority were able to perform full or modified duty at all times. At the beginning of the period of observation retrograde lymphangitis, lymphedema and lymphadenitis were relatively prevalent, but with the passage of time the incidence of these findings greatly decreased until there was difficulty in establishing a diagnosis of filariasis. Frequently a palpable lymph node was the only remaining evidence of infection. However, since lymphadenopathy was encountered just as frequently in patients with malaria and active fungus infections, Coggeshall concluded that lymphadenopathy alone could not be used as a diagnostic criterion for filariasis.

The experience at Klamath Falls was also written about by Haviland and by Zeligs and again at a later date by Coggeshall. They concluded that filariasis in a nonendemic area had a self-limited course and after one or more reactivations died out. Reactivations were characterized clinically by mild fever, local redness and swelling, retrograde lymphangitis and lymphadenitis. They suggested that such symptoms might be due to development of an adult worm in a lymph vessel with subsequent inflammation. Zeligs found that severe or incapacitating sequels occurred in only 0.2 per cent of Marines with filariasis, and believed that spontaneous recovery would occur in most patients.

Behm and Hayman made an "interim report on the history and condition of 542 men 2 years after leaving Tonga-Tabu, a highly endemic area, where they had been on duty from May 1942 to May 1943." A report of the symptoms which developed in these men late in 1943 had been previously published (23). When observed by Behm and Hayman the positive physical findings in the 532 men were: axillary adenitis, 167; epitrochlear adenitis, 62; inguinal adenitis, 272; femoral adenitis, 167; enlarged epididymis or testicle, 34; thickened spermatic cord, 63; and chronic lymphangitis, 5. They found that the incidence as well as the severity of symptoms rapidly diminished during 1945, which was about 3 years after the first exposure to filariasis. Persistent disabling symptoms were present in 3 patients—1 with persistent lymphedema of both legs, 1 with a lymph scrotum, and 1 with recurrent lymphangitis. Most men were free of symptoms after they had been out of the endemic area 20 months.

Diagnosis. "The diagnosis of early filariasis is difficult. Demonstration of microfilariae or adult worms in biopsy material is the only documentary evidence. The observation of a typical attack of 'mumu', with fever, lymphadenopathy and retrograde lymphangitis is convincing. In patients removed from an endemic zone, where diagnosis must be based on history, symptoms, and minimal physical findings, a careful appraisal is essential. The skin test is helpful, but eosinophilia or other laboratory examination is of no value. It

must be determined whether the man has been in an endemic area. All other discoverable causes for the symptoms should be excluded. The emotional status of the patient must be appraised."

This quotation from Behm and Hayman is a good summary of the problem of diagnosis. They state further, "A considerable number of troops stationed in certain parts of the Pacific area have been infected with filariasis during this war. Due to the unfamiliarity of most physicians with the early manifestations of the disease, the diagnosis has been made not only in men who have never been in an endemic area, but in many others whose symptoms were due to a variety of causes. Men have been sent to this hospital with a diagnosis of filariasis who suffered from angioneurotic edema, thrombophlebitis, lymphogranuloma venereum, epididymitis secondary to prostatitis or urethritis, and a variety of similar conditions. In our opinion the occurrence of muscle pains, nocturnal orchiodynia or numbness in an extremity, even in men who have been in an endemic area, is not evidence of filarial infection. Too much emphasis cannot be laid on the fear, worry, and anxiety produced in men when the suggestion of possible filarial infection is made."

Prognosis. Sufficient information is now at hand to justify a favorable prognosis. The facts which support this view have been given in the original papers (19, 21, 51, 54) and summarized earlier in this paper (Follow-up Studies). They indicate that in most cases signs and symptoms disappeared within 20 months after patients left the endemic area.

Treatment. Removal to a nonendemic area was the first step in the treatment of early filariasis in American Armed Forces. During acute exacerbations in nonendemic zones simple rest for a few days with prompt return to duty was recommended (51). The program instituted at Klamath Falls by the Naval Bureau of Medicine and Surgery (54) consisted of "a combined program of military, vocational, educational and medical training and supervision."

Laboratory Findings

Microfilariae in Blood and Hydrocele Fluid. Microfilariae were not found in peripheral blood in the great majority of cases (14, 5, 24, 32, 48, 17, 15, 9, 43, 41, 53, 54). Blood was taken from many thousands of patients at all times of the day and night and examined by all known methods without finding microfilariae. Flynn wrote "a total of 8 cases or 6.4 per cent showed blood or lymph node aspiration material positive for microfilariae . . . . The ones with positive blood were in the first few groups," and later "no more blood positive cases were received."

Recently microfilariae have been found in at least 8 patients (23, 30, 19, 51). Hodge, Denhoff and Vanderveer found 2 microfilariae in over 2000 blood samples, taken from 266 soldiers. Leede and Josey found microfilariae once in an individual who had lived for years in an endemic zone in childhood, and stated that in another patient microfilariae were demonstrated in an overseas hospital. Goodman, Weinberger, Lippincott, Marble and Wright examined the blood of 145 men on 7 nights and 3 days by the Knott concentration method and dis-

covered microfilariae in 2 instances. The observation was true once in each patient. In 2 other patients, microfilariae had been found in the blood overseas on one occasion each. None of these authors identified the species of microfilaria and only Hodge, Denhoff and Vanderveer described the organisms which were observed. They saw oscillating motion within the sheath in 1 instance and in another sluggish bending motion of the posterior third of the body for a short time. Behm and Hayman wrote that "no microfilariae were found in any of these groups (709 patients) while at the hospital (Moore General Hospital, Swannanoa, N. C.). Microfilariae had been repeatedly demonstrated, however, in one man of group A while on Woodlark, and in a second before arrival at this hospital. Neither of these men were available for study. In addition to these 2, the records of 2 other men of group A recorded the finding

TABLE VII

Laboratory Data

Legends are the same as in Table II.

	AUTHOR'S REFERENCE NUMBER																	
	14	5	24	16	32	48	17	15	8	43	23	41	19	30	45	51	53	55
Microfilaria in blood (number of cases)	0	0	0	8	0	0	0	0	0	0	2	0	4	2	0	4	0	0
Skin test (per cent positive)	83	35	83		87	91					63	+++	54-77	88	+++	79.5		85
Eosinophilia (per cent of cases)		++		5	10	67		44	+		19	60	70	0	34	+	40	+
Number of biopsies with parasites	0	2			40	5					1	0	0			3	0	0
Number of biopsies with tissue lesions				24							7	24	19				0	
Number of biopsies without tissue lesions							2										4	
Total number of biopsies	17	8		59	120	17	2				8	30	19			20		

of a single microfilaria on one examination. These two were examined repeatedly over a period of several months, but no microfilariae could be found." Presumably these are the same patients described by Hodge, Denhoff and Vanderveer. In addition, Behm and Hayman mention "one soldier who served in another endemic area . . . who has never had any symptoms but shows large numbers of microfilariae in his blood." No photomicrographs of the microfilariae have been published.

Hydrocele fluid was examined by several authors (48, 53) but no microfilariae were found.

Biopsies. A total of 364 biopsies were reported including those at the Army Institute of Pathology and adult worms or microfilariae were found in 78 (22 per cent) of them (14, 16, 32, 48, 17, 5, 23, 41, 19, 4, 51, 53). Dickson, Huntington and Eichold, Michael, and Hodge, Denhoff and Vanderveer, recovered entire living specimens which were positively identified as adult *Wuchereria*

bancrofti. The other authors identified the worms with reasonable certainty as *W. bancrofti* from examination of serial tissue sections. Behm and Hayman found a microfilaria in a thrombosed lymph vessel. No *Wuchereria malayi* were found. Most authors held the opinion that biopsies of lymph nodes and lymph vessels might be taken safely from the extremities, and some even thought that biopsies from these locations might be beneficial because infective organisms were removed. However, several authors (17, 22) cautioned against taking biopsies of inguinal and femoral lymph nodes or of the genitalia because adverse results had been observed.

Leukocytes. According to reported data the total white blood cell count averaged about 9,000 with extremes of 3,600 and 19,000 per cu. mm. There was no significant alteration of the total number or form of neutrophils, lymphocytes, or mononuclear cells. Eosinophilia occurred in one-half to two-thirds of the cases, the average being about 850 cells per cu. mm. Most authors thought that the presence of eosinophilia was not helpful in diagnosis. Eosinophilia was not observed in Leede and Josey's patients. The results of Hodge, Denhoff and Vanderveer were not in agreement with this. Their data suggested that the incidence of eosinophilia (9 per cent or above) was significantly greater in soldiers exposed to filariasis than in those living in the tropics but not exposed to the disease. In exposed troops with signs of filariasis, the incidence of eosinophilia was greater than in those with no evidence of disease. In soldiers with slight or doubtful filariasis the incidence of eosinophilia was twice as great as in those with frank clinical filariasis.

Red Blood Cells. No abnormalities of red blood cell count or hemoglobin were attributed to filariasis.

Sedimentation Rate of Red Blood Cells. This was normal in the patients studied by Goodman, Weinberger, Lippincott, Marble and Wright. King reported that it was normal in 6 cases and slightly elevated in 2 (Wintrobe method). Saphir found that the sedimentation rate was normal in 28 cases, elevated to 15 to 20 mm. per hour in 6 cases, and 29 mm. per hour in 1 case.

Urine. The urine was normal and no case of chyluria was seen (27, 23, 19). This was in keeping with the usual experience with the non-periodic type of filariasis. Urine cultures were negative for pathogens in several patients (23).

Stool Examinations. Dickson, Huntington and Eichold found parasitic ova in the stools of 14 per cent of their patients. Huntington, Fogel, Eichold and Dickson reported the same incidence and Thompson, Rifkin and Zarrow 15 per cent. Michael stated that of 307 patients none showed ova or parasites. Saphir found none in his 35 cases. Twenty-five per cent of Wartman and King's patients had parasites in their stools. The following parasites have been reported: *Necator americanus, Trichuris trichiura, Ascaris lumbricoides, Enterobius vermicularis, Endamoeba coli,* and *Hymenolepis nana.*

Bacterial Cultures. Bacterial cultures of biopsy material were made by many workers (24, 32, 47, 41, 23). With the exception of one node from which Michael isolated *Staphylococcus albus,* all reported results are negative. Tissue sections stained for acid-fast and gram positive and negative bacteria were

negative (47, 41). Hodge, Denhoff and Vanderveer cultured blood, aspirated fluid from lymph nodes, hydroceles, and a prepatellar bursa but pathogens were never isolated. They also reported that prostatic smears in their patients were negative. It was thus evident that bacteria were not associated with filarial lymphangitis and lymphadenitis in the armed forces.

Microfilariae in the Blood of Natives. Several authors made surveys of natives who were living in the areas where the troops were infected (Fig. 12). Dickson, Huntington and Eichold, and Huntington, Fogel, Eichold and Dickson found 13.6 per cent of natives harbored *Microfilaria bancrofti*, non-periodic variety; Johnson reported an incidence of 80 per cent and Englehorn and Wellman, 40 per cent. Lowman found an incidence of 15.9 per cent. The greatest incidence was in the age group 20–35 years and males were infected twice as frequently as females. One child of 2 years and another of 3 years 3 months were found infected. Wartman and King examined several blood smears of natives of Wallis Island and found *Microfilaria bancrofti*.

Intradermal Tests. It is not the purpose of this paper to give a critical review of sero-reactions in filariasis and the interested reader is referred to original sources (3, 24, 19). Our concern is simply to describe the findings which have been reported for American Armed Forces.

The results of intradermal testing with *Dirofilaria immitis* antigen were reported by many authors (14, 5, 24, 32, 48, 30, 19, 51, 54). Dickson, Huntington and Eichold tested 137 patients with *Dirofilaria immitis* antigen and obtained positive immediate and delayed reactions in 83 per cent. They stated that "the total maximum dose and the volume of fluid injected were considerably less than those advocated by Fairley."

Burhans, Camp, Butt and Cragg stated that in the majority of their cases "*Dirofilaria immitis* skin tests for filaria had been done in the islands and reported as positive in 16 cases."

Huntington, Fogel, Eichold and Dickson used "an extract of the dog heartworm, *D. immitis*" and considered the test positive only if both immediate and delayed reactions were positive. They found that the test was positive in 83 per cent of filariasis cases and 5 per cent of their control series. "Tests with Ascaris extract showed some degree of cross-reactivity between Ascaris and Dirofilaria." The tests "did not correlate closely with clinical activity, since many men who had been in the area for many months had positive skin tests before they developed mumu." They concluded that patients with filariasis were sensitized to filarial substance. The fact that there was a low incidence of intestinal parasitism suggested that the sensitivity was not due to other helminths. They made the interesting observation that particularly severe cases of mumu produced desensitization and speculated that this was the explanation for negative reactors.

Michael used the "identical technic and the same type of antigen of *Dirofilaria immitis*" as Huntington, Fogel, Eichold and Dickson and found 87 per cent positive immediate and delayed reactions in 307 known filariasis patients.

The papers of Wartman and King, and King, give [illegible] data

experiences with intradermal testing in filariasis. They injected 0.1 ml. of a 0.1 per cent saline extract of dried *D. immitis* obtained from infected dogs in Townsville, Australia. Positive reactions occurred in 91 per cent of patients with filariasis and in 11 per cent of the control series of normal persons. They also tested 241 Marines who had been in Samoa and Wallis Islands for several months but had not developed clinical signs of filariasis, and 108 (45 per cent) gave a positive reaction. Although none presented evidences of filariasis when the tests were done some later developed clinical filariasis. There was no significant difference in reaction between patients with intestinal parasites (*N. americanus*, *T. trichiura*, *H. nana*, *A. lumbricoides*, *E. vermicularis*) and patients without intestinal parasites (3 examinations on different days by the $ZnSO_4$ sedimentation method). Thus, 47 patients with positive stools had 93.6 per cent positive skin reactions and 114 patients with negative stools had 91.2 per cent positive skin tests. This evidence suggested that positive reactions obtained with *D. immitis* antigen are seldom caused by other helminths.

Huntington studied the intradermal tests in (1) troops newly arrived in an endemic area, (2) in troops with several months residence and vague or uncertain symptoms, and (3) in men with outspoken clinical mumu. In the first group of 128 patients the test was positive in only 5 per cent, in the second in 74 per cent, and in the third group of 202 patients in 83 per cent. Weak or negative skin tests were consistently observed in severe cases of mumu, and in a few cases a certain amount of desensitization was achieved by repeated doses of extract. Sometimes the desensitization was sharply localized to the affected arm. There was no reaction to a 1:200 saline extract of powdered heart muscle, but occasionally there was cross reaction to a similar extract of *Ascaris lumbricoides*. Guinea pigs were sensitized by injections of 0.025 mg. to 2.5 mg. of dried *D. immitis* powder suspended in oil or saline on three occasions at intervals of a week or more. The animals and a group of normal controls were then tested with 0.2 cc. of 1:200 saline extract of *D. immitis* injected intradermally. Sensitized animals reacted more readily and more severely than control animals.

On the basis of this work, Huntington concluded that "the skin test results accord well with epidemiologic data (7), mosquito studies, the characteristic histologic picture, the absence of demonstrable bacterial infection in mumu, and the finding of filariae in excised tissue." "The fact that reactions quite comparable to natural mumu can be elicited with Dirofilaria extracts supports the belief that Wuchereria are themselves capable of producing inflammatory reactions, and that at least some of the clinical pictures of filariasis are correctly designated and are not due primarily to bacterial infection." "The entire body of evidence supports the belief that the highly characteristic clinical entity of mumu is, as Buxton and Hopkins suspected, of filarial origin."

Huntington believed that although the skin test was "helpful in the general study of etiology of mumu, (it) is not particularly helpful in the diagnosis of individual cases. With the cross reactivity with other helminths, the occurrence of sensitization in preclinical or subclinical infection, and of desenstitization

in particularly severe cases (and some others), ambiguities of interpretation appear greater with the skin test than with the clinical picture."

Zarrow and Rifkin used a *D. immitis* antigen prepared according to the method of Dickson, Huntington and Eichold with certain modifications (acetone and saline extractions). Five hundredths ml. of a saline extract in dilutions of 1:2000, 1:4000, 1:8000 and 1:16000 were injected into the skin of the volar surface of the arm. A control was also used consisting of an extract of heart muscle treated the same as the *D. immitis* antigen. In one series of 91 patients with clinical filariasis 94 per cent gave a positive reaction to a dilution 1:4000 or above. In another group of 53 patients, of which 60 per cent were proved by biopsy, 73 per cent gave a positive reaction to the 1:4000 antigen. In 3 cases a positive biopsy was obtained with a negative skin test. They suggested these were cases in which desensitization had occurred (14).

Leedo and Josey used a 1:8000 dilution of antigen prepared from horse filaria (*Setaria equina*) and dog heartworm (*Dirofilaria immitis*) by Bozicevich of the National Institute of Health. Dog and horse protein as well as saline controls were used. Eighty-eight per cent of filariasis patients gave positive reactions. Of 49 normal, non-allergic individuals from Northern United States without tropical service 14 per cent gave false positive reactions.

Goodman, Weinberger, Lippincott, Marble and Wright made a thorough study of the intradermal test in 145 patients with clinical filariasis in whom adult worms were not found in biopsies although microfilariae were found in the blood of 4 of them. They used as antigens 1:8000 dilution of *Dirofilaria immitis* and of *Setaria equina*, and 1:2000 dilution of *Litomosoides carinii*. The antigens were prepared at the National Institute of Health. Control antigens of dog and horse serum proteins in dilutions corresponding to that of the filarial antigens were also employed. Direct intracutaneous tests with the *D. immitis* and *S. equina* antigens gave positive responses in 54 per cent of cases as compared with 6 per cent in 106 control subjects. Of 75 patients tested with *L. carinii* antigen, 77 per cent gave positive reactions. In passive transfer tests positive responses were obtained to either or both *D. immitis* or *S. equina* antigen in 1:8000 dilution in 29 per cent of cases. Of 50 patients tested with 1:200 dilution of *L. carinii*, 46 per cent gave positive reactions.

Hodge, Denhoff and Vandervcer, not being able to get suitable antigens for skin testing, prepared a saline extract of an epitrochlear lymph node which had been digested with 0.6 per cent pepsin in 0.3 per cent HCl at 37°C. for 12 hours, and then treated with acetone and ether until a powder was obtained which was diluted 1:20 with saline. Adult filariae were not found in the node, but it was from a patient who had superficial lymphangitis of the arm and 17 per cent eosinophilia and was in an endemic area. Eleven patients with clinical filariasis were tested by injecting 0.1 ml. of the extract subcutaneously and 7 (64 per cent) showed positive reactions. Fifteen patients not exposed to filariasis were also tested and gave negative reactions.

Culbertson, Rose and Demarest used an antigen made from *Litomosoides*

carinii, a filarial worm found naturally in the cotton rat (*Sigmodon hispidus*). One-tenth milliliter of a 1:200 saline dilution of dried worm was injected intradermally into 81 soldiers who had clinical evidences of filariasis and a history of exposure for about 12 months in the South Pacific area, but with negative blood smears and biopsies. Sixty-six (81 per cent) gave immediate skin responses.

Bozicevich and Hutter claimed that by using antigens of *D. immitis* in 1:8000 dilution false positive reactions were reduced without increasing the number of false negative reactions. However, their claim that 1:1000 dilution of antigen gave false positive reactions in approximately 30 per cent of non-exposed individuals was not supported by the work of other investigators. They also noted that in some cases (15 of 25 patients) injections of 1:8000 dilution of antigen was followed by exacerbation of symptoms of lymphangitis together with pain in the scrotum and inguinal nodes.

Behm and Hayman reported positive skin tests in 75.5 per cent of 196 patients with filariasis. In a second group of 336 men, who had been exposed to filariasis but in whom an objective clinical diagnosis could not be made, 42 per cent had positive skin tests. In a third group, in which there was a history of questionable exposure to filariasis but absence of physical signs, the skin test was positive in 19.1 per cent of individuals. They estimated that the incidence of false positive tests was 6 per cent. The antigen used was 1:8000 *D. immitis* prepared according to the technique of Bozicevich and Hutter. They thought the findings in the second group (336 men) might be due to "biological" infections, that is infections sufficient to produce skin sensitivity, but not symptoms. There was no explanation for the third group in which there was apparent increased sensitivity in men who had had tropical service. They pointed out that it decreased the value of the test.

Gonzales and Morales tested 36 soldiers and sailors who had been recently transferred from continental United States to Puerto Rico, with 1:200, and 1:10,000 dilutions of saline antigens prepared from *L. carinii*, *D. immitis* and from microfilariae of *W. bancrofti*. The patients had no clinical or laboratory evidence of filariasis and no intestinal nematodes. All gave negative reactions. Two men gave positive reactions to *A. lumbricoides* antigen. In a group of 45 native Puerto Ricans harboring microfilariae of *W. bancrofti* but without clinical symptoms 41 (94 per cent) gave positive reactions. Of another group of 40 Puerto Ricans without blood microfilariae or clinical filariasis, 35 (87 per cent) gave positive reactions.

Passive Transfer Tests (Prausnitz-Küstner Reaction). In 30 patients in whom passive transfer tests were done by Goodman, Weinberger, Lippincott, Marble and Wright, 8 or 27 per cent gave positive wheal reactions with *L. carinii* antigen (1:200 dilution) and 5 or 17 per cent with Ascaris extract (1:100 dilution).

Bozicevich and Hutter elicited local passive hypersensitivity in 4 of 6 recipients injected with the blood serum of filariasis patients. They used 1:8000 dilution of *D. immitis* antigen.

Intracutaneous Tests with Antigens of Other Nematodes. Gonzales and Morales reported that in 90 Puerto Ricans with microfilariae of *W. bancrofti* in their

blood 85 per cent and 7 per cent reacted to 1:10,000 dilutions of Ascaris and of hookworm antigens respectively. Approximately the same figures were obtained in natives without circulating microfilariae. However, in 35 soldiers who recently arrived in Puerto Rico, 12 per cent reacted to Ascaris, but none to hookworm antigens.

Huntington, Fogel, Eichold and Dickson also reported cross reactivity with Ascaris antigens in some patients.

Bozicevich and Hutter reported that of 25 patients with filariasis 3 (12 per cent) gave positive reactions to *Trichinella spiralis* antigen, but in the control series of 6 malaria patients 1 (15 per cent) gave a positive reaction. Of 6 patients sensitized by injection of blood serum from filariasis patients 24 hours before, 1 reacted positively to *T. spiralis*.

Goodman, Weinberger, Lippincott, Marble and Wright reported that 3.5 per cent of their cases of filariasis reacted positively to 1:8000 dilution of *T. spiralis* antigen. These same patients had positive tests with 1:8000 *D. immitis* antigen. Forty-seven patients tested with *A. lumbricoides* extract in 1:100 dilution gave immediate positive wheal reactions in 42 per cent. Eighty-nine per cent of the same patients gave positive reactions with 1:200 *L. carinii* antigen. In passive transfer tests in 30 patients 5 (17 per cent) gave positive immediate reactions with Ascaris extracts. They also tested 84 patients with Frei antigen (lygranum) and observed 2 positive reactions. In this same group of cases approximately 50 per cent gave positive reactions with *D. immitis* antigen in 1:8000 dilution and 89 per cent gave positive reaction with *L. carinii* in 1:200 dilution.

Seroreactions. Complement fixation tests using a saline extract of *D. immitis* were positive in 66 per cent of 143 patients with filariasis, but the test was also positive in 16 to 25 per cent of normal control subjects (19). There was agreement between the results of complement fixation tests and the direct intracutaneous tests with *S. equina* and *D. immitis* in 71 per cent of patients. In another series negative complement fixation tests were obtained in 25 patients who had a positive intradermal test with *D. immitis* antigen. An antigen of *D. immitis* in dilution from 1:100 to 1:600 was used. Alcoholic antigens were inferior to saline antigens (3).

Culberston, Rose and Demarest using a 1:125 dilution of *L. carinii* antigen obtained fixation of complement in 59 of 77 patients (76.6 per cent). Using the same antigen they found 58 (75.3 per cent) of these patients had positive precipitin tests.

Oliver-Gonzales and Bercovitz using microfilariae of *W. bancrofti* as an antigen found strong positive precipitin reactions in 2 of 26 patients with circulating microfilariae, but without symptoms and in 3 of 14 patients without circulating microfilariae but with clinical filariasis.

Hayman, on the basis of his experience at the Tropical Disease Service at Moore General Hospital, was of the opinion that neither complement fixation nor precipitin tests gave reliable results.

The Kahn test was negative in 35 (100 per cent) of Saphir's patients.

King reported that the Kahn reaction was negative in 26 patients and that

heterophile antibody agglutinations were within normal limits in 4 patients. Damin and Weller determined heterophile antibody agglutinin and cold autohemagglutinin titers in 104 cases of filariasis with negative results. Thirteen per cent of patients had a heterophile agglutinin titer above 1:32.

Roentgenograms. X-ray studies of patients with filariasis failed to reveal calcified worms. King took x-rays of the soft tissues of 9 cases with lymphangitis or epitrochlear lymphadenopathy, and of the scrotum of 5 patients with epididymitis and funiculitis, with negative results in all. Goodman, Weinberger, Lippincott, Marble and Wright took roentgenograms of the scrotum in 29 cases and found small areas of increased density ranging from 1 to 3 mm. in diameter in 4 patients. However, they were not certain that such calcification was due to *W. bancrofti*.

PATHOLOGIC LESIONS DESCRIBED IN THE LITERATURE

Michael, Wartman, and Rifkin and Thompson, have given detailed descriptions of the pathologic lesions in lymph vessels and nodes, and others have given briefer accounts (5, 14, 16, 23). As a result of these studies it was clear that adult filaria worms in the lymphatic system might cause an inflammatory reaction which was essentially granulomatous in nature. There was necrosis and great proliferation of macrophages, giant cells, and reticular fibers around the worms, and usually large numbers of eosinophils. These changes were often not limited to the immediate vicinity of the worms but were present throughout the nodes. Hyperplasia of littoral cells of medullary and subcapsular sinuses was frequently striking and in such cases the exudation of eosinophils was likely to be extraordinary especially if necrosis had occurred. Such foci have been referred to as "eosinophilic abscesses." Repair consisted of growth of fibroblasts and mature connective tissue around the worms resulting in cicatrization and calcification.

Michael believed that the sex of the infecting worm might influence the histologic changes. He found that solitary male or female worms began to degenerate in 2 to 6 months and that this was accompanied by the appearance of clinical symptoms. Male worms degenerated somewhat earlier and faster than females. When male and female worms lay close together and fertilization took place, degeneration did not occur until later, often at the time of parturition and hence the onset of clinical symptoms was delayed. Changes in the worms themselves accompanied the changes in the surrounding tissues. Cloudy swelling and pyknosis of ovarian and testicular cells of the worms was followed by necrosis and calcification of all viscera. Saponification and calcification of the cuticle and eventual absorption of the parasite terminated the process.

Many of the changes which have been described as occurring in worm infested lymph nodes were also observed in tissues in which no parasites were discovered even in serial sections. It was further recognized that during an attack of lymphangitis distant nodes might enlarge. Biopsies of such nodes at the height of enlargement showed marked hyperplasia, infiltration of eosinophils, and dis-

tention of lymphatic sinuses. No parasites were found (33). Such lesions have been accounted for by many authors on an allergic basis.

Changes in lymph vessels consisted of dilatation, lymph thrombosis and acute lymphangitis which was sometimes necrotizing. In some cases these changes were apparently reversible, but in others fibrosis and obstruction of the affected lymphatic vessel ensued (47).

Biopsies of fugitive or transitory swellings showed vascular engorgement with edema and infiltration of round cells around lymph and blood vessels. Eosinophils were numerous and there was hyperplasia of endothelial cells. No parasites were discovered. These lesions occurred either before, during, or after an attack of lymphangitis and were not affected by epinephrine (33).

Biopsies of skin at the height of the delayed reaction (about 24 hours) to *Dirofilaria immitis* antigen showed a microscopic picture which was very similar to that seen in biopsies of fugitive swellings. In addition, there was edema and round cell infiltration of the epidermis and engorgement of vascular channels. Eosinophils were present throughout the cutis (33).

The only description of the pathologic lesions in the genitalia was given by Michael, who examined sections of the tissues of patients with enlargement of testis and spermatic cord and noted that they only showed "sensitivity changes." He was unable to find either adult or larval worms. He described the autopsy of a Marine, 50 years old, who had filariasis and died of coronary occlusion. There was diffuse edema and cellular infiltration of spermatic cord, epididymis and testis. Many lymphatic vessels were thick, dilated and surrounded by lymphocytes and eosinophils. Serial sections of the entire specimen failed to disclose parasites. However, adult *W. bancrofti* were found in the lymphatics of the arm.

From these observations Michael speculated that many genital enlargements are toxic or allergic in nature and not due to direct invasion of the organs by parasites. Therefore, the changes were presumed to be reversible and normal tissue integrity could be restored. Sterilization, if it occurred at all, should not be permanent. No secondary sex changes were observed, even though the interstitial tissues of the testes were the seat of the main reactions.

Results of the Present Study

Material available for study at the Army Institute of Pathology consisted of biopsies of epididymis, spermatic cord, testis, lymph node and lymph vessel. There was no autopsy material. In the section which follows, the general tissue changes found in the various organs will be described. The individual case reports and microscopic slides are on file at the Army Institute of Pathology, Army Medical Museum, Washington 25, D. C. Table VIII gives the pertinent data for these cases.

Epididymis

Microscopic sections of epididymis were available in two cases (Case 1, 2). Both patients were male Puerto Ricans who presumably had been infected in

TABLE VIII

Summary of Cases at Army Institute of Pathology

CASE	AGE	COLOR	CLINICAL DIAGNOSIS	PLACE INFECTED	EXPOSURE FROM—TO	ONSET	MFL. IN BLOOD	SKIN TEST	BIOPSY	LESIONS	A.I.P. ACCESSION NUMBER
1	18	Puerto Rican	Chronic right orchoepididymitis	Puerto Rico	Life 1924–?	1940–1942			Testis, epididymis	W*	86686
2	37	Puerto Rican	Chronic epididymitis, bilateral	Puerto Rico	Life 1906–?	2 years ago	0		Epididymes	W	101611
3	31	White	Acute funiculitis	South Pacific	Present war	1944			Spermatic cord	W M	110147
4	22	Chinese	Acute funiculitis	China	Life	1943			Spermatic cord	W	96815
5	18–26	White	Acute lymphangitis, left arm. Acute left epitrochlear and femoral adenitis	Wallis Island	May 1942 Sept. 1942	3–13 + months	0	+	Left epitrochlear node	W	Wartman Case 41
6	18–26	White	Acute lymphangitis, left arm. Acute left epitrochlear adenitis	Wallis Island	May 1942 Sept. 1942	3–13 + months	0	+	Left epitrochlear node	W	Wartman Case 453
7	18–26	White	Acute lymphangitis, right arm. Acute right epitrochlear, axillary and inguinal adenitis	Wallis Island	May 1942 Sept. 1942	3–13 + months	0	+	Right epitrochlear node	W	Wartman Case 512
8	18–26	White	Acute epitrochlear adenitis, bilateral	Wallis Island	May 1942 Sept. 1942	3–13 + months	0	+	Right epitrochlear node	W	Wartman Case 771

9	29	White	Lymphedema scrotum Right epitrochlear and inguinal adenitis	Samoa		21 March 1944			Right epitrochlear and inguinal nodes	W	110940
10	18	Puerto Rican	Femoral adenitis Acute lymphangitis, both legs Filarial fever	Puerto Rico	1926–1941	1942	+		Femoral lymph node	W	106213
11	21	Chinese	Femoral adenitis Filarial fever	China	1922–1943	24 Feb 1943			Femoral lymph node	W	91550
12	18–26	White	Acute axillary adenitis, bilateral	Wallis Island	May 1942 Sept 1942	3–13 + months	0	+	Axillary node	T	Wartman Case 461
13	18–26	White	Acute lymphangitis, arms bilateral	Wallis Island	May 1942 Sept 1942	3–13 + months	0	+	Axillary node	T	Wartman Case 462
14	18–26	White	Acute lymphangitis, right arm Right epitrochlear and axillary adenitis	Wallis Island	May 1942 Sept 1942	3–13 + months	0	+	Right epitrochlear node	T	Wartman Case 473
15	18–26	White	Acute epididymitis, right Acute inguinal and femoral adenitis	Wallis Island	May 1942 Sept 1942	3–13 + months	0	+	Inguinal lymph node	T	Wartman Case 479
16	18–26	White	Acute left epididymitis Acute left inguinal adenitis	Wallis Island	May 1942 Sept 1942	3–13 + months	0	+	Inguinal lymph node	T	Wartman Case 487

*W = worms, M = microfilariae, T = typical tissue reaction, O = neither organisms nor tissue reaction

TABLE VIII—*Continued*

CASE	AGE	COLOR	CLINICAL DIAGNOSIS	PLACE INFECTED	EXPOSURE FROM—TO	ONSET	MFL. IN BLOOD	SKIN TEST	BIOPSY	LESIONS	A.I.P. ACCESSION NUMBER
17	18–26	White	Acute lymphangitis, left arm. Acute right epitrochlear and axillary adenitis. Acute right epididymitis and funiculitis	Wallis Island	May 1942 Sept. 1942	3–13 + months	0	+	Left epitrochlear lymph node	T	Wartman Case 569
18	18–26	White	Acute lymphangitis, both arms. Acute epitrochlear adenitis, bilateral	Wallis Island	May 1942 Sept. 1942	3–13 + months	0	–	Left epitrochlear lymph node	T	Wartman Case 633
19									Lymph node	T	121066
20	34	Black	"Filariasis"	South Pacific	1 year	Oct. 1943			Epitrochlear lymph node	T	102536
21	39	White	"Filariasis"	Cook Island		Oct. 1943			Inguinal lymph node	T	117466
22	23	White	"Filariasis"	Tonga Tulu New Hebrides	6 mo. 1942 2½ mo. 1942	1942			Lymph node	T	121595
23	23	Black	Filariasis			1 mo.			Inguinal lymph node	T	102539
24	18–26	White	Acute lymphangitis, left arm. Acute epitrochlear adenitis	Wallis Island	May 1942 Sept. 1942	3–13 + months	0	+	Left epitrochlear lymph node	T	Wartman Case 454

25	18–26	White	Acute left epididymitis Acute left inguinal adenitis	Wallis Island	May 1942 Sept 1942	3–13 + months	0	+	Left inguinal lymph node	0	Wartman Case 188
26	18–26	White	Acute epididymitis, right with lymph scrotum Acute right inguinal adenitis Left hydrocele	Wallis Island	May 1942 Sept 1942	3–13 + months	0	+	Right inguinal lymph node	0	Wartman Case 494
27	18–26	White	Acute lymphangitis, left arm Acute epitrochlear adenitis, bilateral	Wallis Island	May 1942 Sept 1942	3–13 + months	0	+	Left epitrochlear lymph node	0	Wartman Case 600 Node Digested
28	24	White	"Filariasis"						Inguinal lymph node	0	120027
29	27	Black	"Filariasis"						Right epitrochlear lymph node	0	102540
30			"Filariasis"	Philippine Island	Many years				Lymph node		52911
31	29	White	Palpable inguinal lymph node and spermatic cord	Aitutaki	Nov 1942 Nov 1943	23 Oct 1943	0	+	Femoral lymph node	0	110282
32	23	White	Palpable inguinal lymph node	Bora Bora	July 1943 Dec 1943	Nov 1943	0	+	Femoral lymph node	0	110282
33	23	White	Palpable inguinal, axillary, cervical lymph	Bora Bora	Feb 1942 Dec 1943	15 Aug 1943	0	+	Axillary lymph node	0	110282

TABLE VIII—*Continued*

CASE	AGE	COLOR	CLINICAL DIAGNOSIS	PLACE INFECTED	EXPOSURE FROM—TO	ONSET	MFL. IN BLOOD	SKIN TEST	BIOPSY	LESIONS	A.I.P. ACCESSION NUMBER
34	21	White	Palpable spermatic cord, inguinal and axillary lymph nodes	Tonga Reva	Nov. 1942 Nov. 1943	18 Oct. 1943	0	−	Left axillary lymph node	0	110282
35	27	White	Palpable spermatic cord, inguinal lymph node	Aitutaki	Nov. 1942 Nov. 1943	28 Nov. 1943	0	+	Right femoral lymph node	0	110282
36	24	White	Palpable spermatic cord, inguinal and axillary lymph nodes	Tonga Reva	Nov. 1942 Nov. 1943	7 Oct. 1943	0	−	Right axillary lymph node	0	110282
37	24	White	Palpable spermatic cord, inguinal and axillary lymph nodes	Bora Bora	Feb. 1943 Dec. 1943	Sept. 1943	0	+	Femoral and inguinal lymph nodes	0	110282
38	24	White	Palpable spermatic cord, inguinal, axillary and cervical lymph nodes	Tonga Reva	Nov. 1942 Dec. 1943	15 Nov. 1943	0	+	Right axillary lymph node	0	110282
39	24	White	Palpable spermatic cord, inguinal and axillary lymph nodes	Aitutaki	July 1942 Nov. 1943	Oct. 1943	0	+	Right femoral lymph node	0	110282
40	27	White	Palpable spermatic cord, and inguinal lymph node	Tonga Reva	Nov. 1942 Jan. 1944	1 Oct. 1944	0	−	Femoral lymph node	0	110282

41	23	White	Palpable spermatic cord, inguinal, axillary, epitrochlear and cervical lymph nodes	Tonga Reva	May 1942 Sept 1943	1 Aug 1943	0	+	Femoral lymph node	0	110282
42	21	White	Palpable spermatic cord	Cook Island	Nov 1942 Nov 1943	12 Oct 1943	0	+	Femoral lymph node	0	110282
43	28	White	Palpable inguinal and epitrochlear lymph nodes	Tonga Island	Nov 1942 Sept 1943		0	+	Epitrochlear lymph node	0	110282
44	28	White	Palpable spermatic cord, inguinal and cervical lymph nodes	British Samoa	Feb 1942 Dec 1943	Jan 1944	0	+	Right axillary lymph node	0	110282
45	21	White	Palpable spermatic cord, inguinal lymph node	Tonga Reva	May 1942 May 1943	13 Oct 1943	0	+	Right axillary lymph node	0	110282
46	20	White	Palpable spermatic cord, inguinal and axillary lymph nodes	Cook Island	Nov 1942 Feb 1944	20 Dec 1943	0	–	Left axillary lymph node	0	110282
47	31		Filarial lymphadenitis	South Pacific					Neck node	T	150262
48	25	White	Generalized lymphadenitis			16 mos ago			Inguinal node	T	150256
49	23	White	Fever Axillary adenitis	South Pacific	7 mos 1942				Right axillary nodes	T	121595
50	21	White	Inguinal lymphadenitis			3 weeks			Right inguinal node	T	153704

TABLE VIII—*Concluded*

CASE	AGE	COLOR	CLINICAL DIAGNOSIS	PLACE INFECTED	EXPOSURE FROM—TO	ONSET	MFL. IN BLOOD	SKIN TEST	BIOPSY	LESION	A.I.P. ACCESSION NUMBER
51	22	White	"Filariasis"	South Pacific		6 mos.			Left axillary node	0	153671
52	27	White	Chronic epididymis						Spermatic cord	T	148685
53	24	White	Filariasis		Long				Inguinal node	0	120027
54									Lymph node	W	151577
55	26	White	Filariasis			Jan. 1944			Right inguinal lymph node	T	131487
56	24	White	Lymphadenitis, right chest wall	Tawara Eniwetok Guam		3 weeks			Node right chest wall	T	148535
57	36	Puerto Rican	Inguinal lymphadenitis			Mar. 1945	0		Inguinal nodes	M	144274
58	30	Black	Inguinal hernia				0	—	Inguinal nodes	T	144275
59	24	Black	Lymphangitis, right leg		5–7 mos.	6 mos.			Right inguinal nodes	T	134534
60	26	White	Chronic funiculitis	South Pacific	23 mos.	2 years			Spermatic cord	T	140988
61	27	Black	Filariasis				0		Epitrochlear node	T	102540
62	24	Black	Acute adenitis, right arm	New Guinea Leyte	12+ mos. Short time	Dec. 1944	0	—	Node right arm	M	141577

63	19	White	Filarial adenitis	South Pacific	Several months	Apr 1945	0		Cervical node	T	148676
64	18–26	White	Acute lymphangitis, left arm Acute adenitis, left axilla Acute epididymitis and funiculitis	Wallis Island	May 1942 Sept 1942		0	+	Left axillary cord	W	Wartman Case 460

Total biopsies with worms	15	23 4%
Total biopsies with lesions, but without worms	25	39 1%
Total biopsies without lesions or worms	24	37 5%
	64	100 0
Total biopsies with lesions	40	62 5%

TABLE VIII—*Concluded*

CASE	AGE	COLOR	CLINICAL DIAGNOSIS	PLACE INFECTED	EXPOSURE FROM—TO	ONSET	MFL. IN BLOOD	SKIN TEST	BIOPSY	LESION	A.I.P. ACCESSION NUMBER
51	22	White	"Filariasis"	South Pacific		6 mos.			Left axillary node	0	153671
52	27	White	Chronic epididymis						Spermatic cord	T	148685
53	24	White	Filariasis		Long				Inguinal node	0	120027
54									Lymph node	W	151577
55	26	White	Filariasis			Jan. 1944			Right inguinal lymph node	T	131487
56	24	White	Lymphadenitis, right chest wall	Tawara Eniwetok Guam		3 weeks			Node right chest wall	T	148535
57	36	Puerto Rican	Inguinal lymphadenitis			Mar. 1945	0		Inguinal nodes	M	144274
58	30	Black	Inguinal hernia				0	—	Inguinal nodes	T	144275
59	24	Black	Lymphangitis, right leg		5–7 mos.	6 mos.			Right inguinal nodes	T	134534
60	26	White	Chronic funiculitis	South Pacific	23 mos.	2 years			Spermatic cord	T	140988
61	27	Black	Filariasis				0		Epitrochlear node	T	102540
62	24	Black	Acute adenitis, right arm	New Guinea Leyte	12+ mos. Short time	Dec. 1944	0	—	Node right arm	M	141577

63	19	White	Filarial adenitis	South Pacific	Several months	Apr 1945	0		Cervical node	T	148676
64	18–26	White	Acute lymphangitis, left arm Acute adenitis, left axilla Acute epididymitis and funiculitis	Wallis Island	May 1942 Sept 1942		0	+	Left axillary cord	W	Wartman Case 460

Total biopsies with worms	15	23 1%
Total biopsies with lesions, but without worms	25	39 1%
Total biopsies without lesions or worms	24	37 5%
	64	100 0
Total biopsies with lesions	40	62 5%

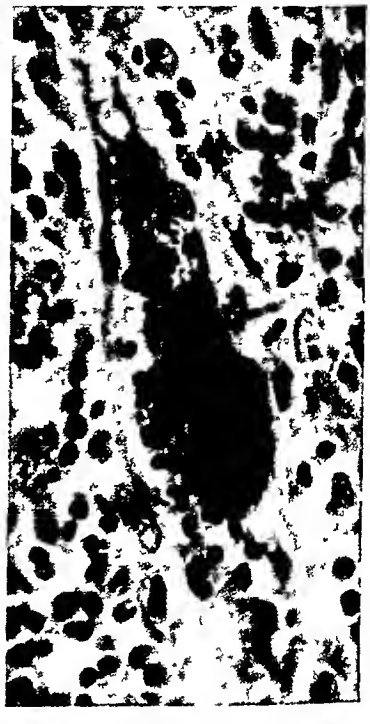


FIG. 1. (Upper left.) Case 9—Accession 110940 Soldier infected in Samoa in 1944. A pregnant female worm, probably *W. bancrofti*, present in an epitrochlear lymph node. There is a characteristic granuloma with acidophilic precipitate and necrosis around the parasite and a peripheral border of macrophages, reticular fibers and eosinophils. H & E ×175.

FIG 2. (Upper right.) Case 62—Accession 141577. Negro soldier, 24 years old, infected in New Guinea in 1944 Granuloma of eosinophils in the wall of one of the sinuses of a lymph node. Microfilariae found in the tissues. See also Figure 4 H & E ×550

FIG. 3. (Lower left) Case 11—Accession 91550. Male Chinese, 21 years old, with long-standing infection. Degenerating adult parasite in a distended lymphatic sinus of a retroperitoneal lymph node. There is eosinophilic precipitate, proliferation of macrophages and giant cell formation around the worm. One of the giant cells has phagocytosed some of the eosinophilic precipitate. Notice that the granuloma projects into the distended lymphatic sinus. Compare with Figure 24. H & E ×160

FIG. 4. (Lower right.) Case 62—Accession 141577. Negro soldier, 24 years old, who was probably infected in New Guinea in 1944. Microfilaria surrounded by basophilic precipitate and lying in the dilated sinus of an inflamed lymph node. In other instances the precipitate was acidophilic as in Figures 18 and 19. H & E ×750.

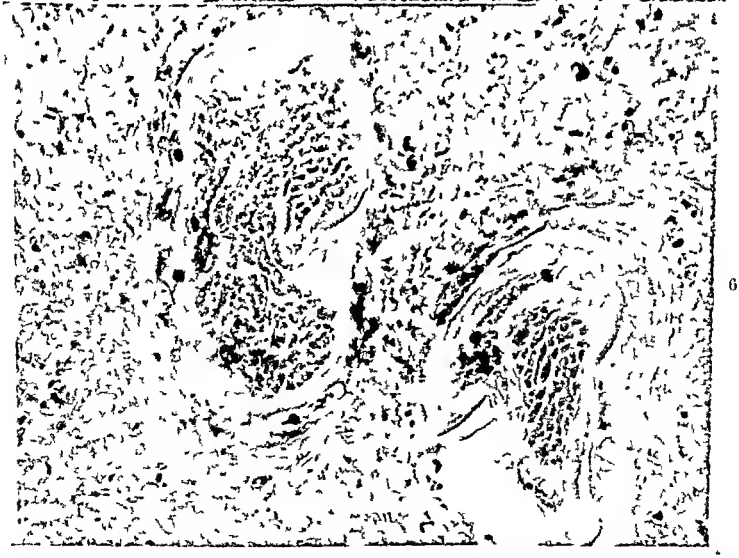
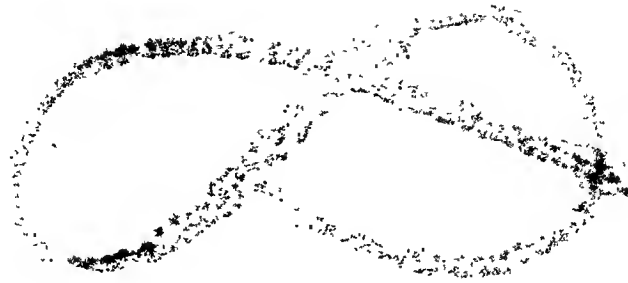
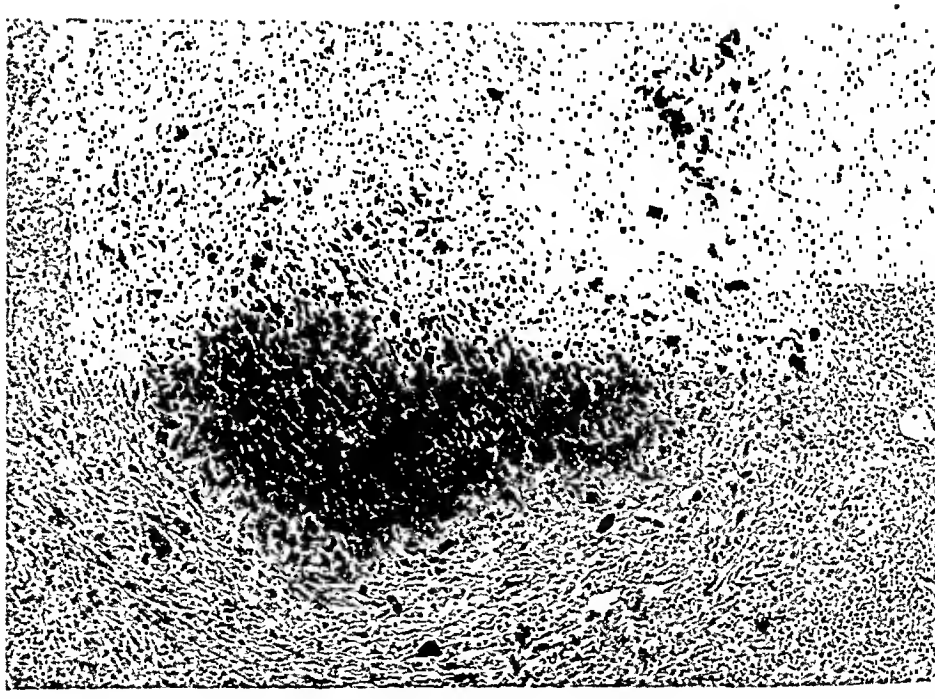


FIG 5 Case 10—Accession 106213 Calcification of adult parasites in a lymph node from a Puerto Rican soldier, 18 years old, with a life long infection The calcified worms are surrounded by dense, avascular collagenous connective tissue and there is infiltration of lymphocytes, plasma cells and occasional eosinophils H & E ×40

FIG 6 Case 9—Accession 110940 High power view of Fig 1 to show the double uterus of the parasite containing numerous uncoiled microfilariae H & E ×600



7



8

FIG. 7. Microfilaria bancrofti, non-periodic variety, in peripheral blood of a native of Wallis Island. Notice the absence of nuclei in the tip of the tail. Compare with Fig. 12. Hematoxylin ×990.

FIG. 8. Case 19—Accession 121066. Granuloma in a lymph node in which no worms were found. Compare this with Figure 1. H & E ×165.

their native country. Adult nematodes were present in one case in the tunica vaginalis and in the other in the fibromuscular tissues of the spermatic cord. The epididymides themselves showed only slight changes such as interstitial

edema and focal exudation of moderate numbers of plasma cells, lymphocytes, eosinophils and histiocytes Often these changes were most marked around lymph vessels. The tubules were well preserved (Fig 33)

In Case 1 several worms, which appeared to be viable, lay in a dilated lymph vessel at the edge of the tunica vaginalis, whereas in Case 2 the worms, which were dead and partly calcified, were situated in the fibromuscular tissue of the spermatic cord (Fig 11) There was a granulomatous type of inflammation with proliferation of macrophages and reticulum, and exudation of eosinophils, plasma cells and lymphocytes In Case 2 considerable amounts of collagenous connective tissue surrounded the dead worms In Case 1 there was involvement of lymph vessels which showed endothelial hyperplasia often of villous character (Fig 29) Strangely, the vessel which contained filarial worms in Case 1 showed the least change

Spermatic Cord

Spermatic cord was included in 5 specimens (Cases 2, 3, 4, 52, 60) In all cases there was marked acute or chronic granulomatous inflammation of the lymph vessels and to a lesser degree of the interstitial tissues, but the vas deferens was spared (Fig 31) This observation supported the clinical impression that filarial funiculitis is in truth filarial lymphangitis of the spermatic cord Case 2 contained calcified worms in the fibromuscular tissue of the spermatic cord as described in the section on epididymis and Case 4 showed adult worms (Fig 10) and larvae in both tissues (Fig 15) and blood (Figs 13 and 14) of a Chinese patient who had in all probability been infected many years before in China. Cases 52 and 60 contained no worms, but there were typical tissue changes

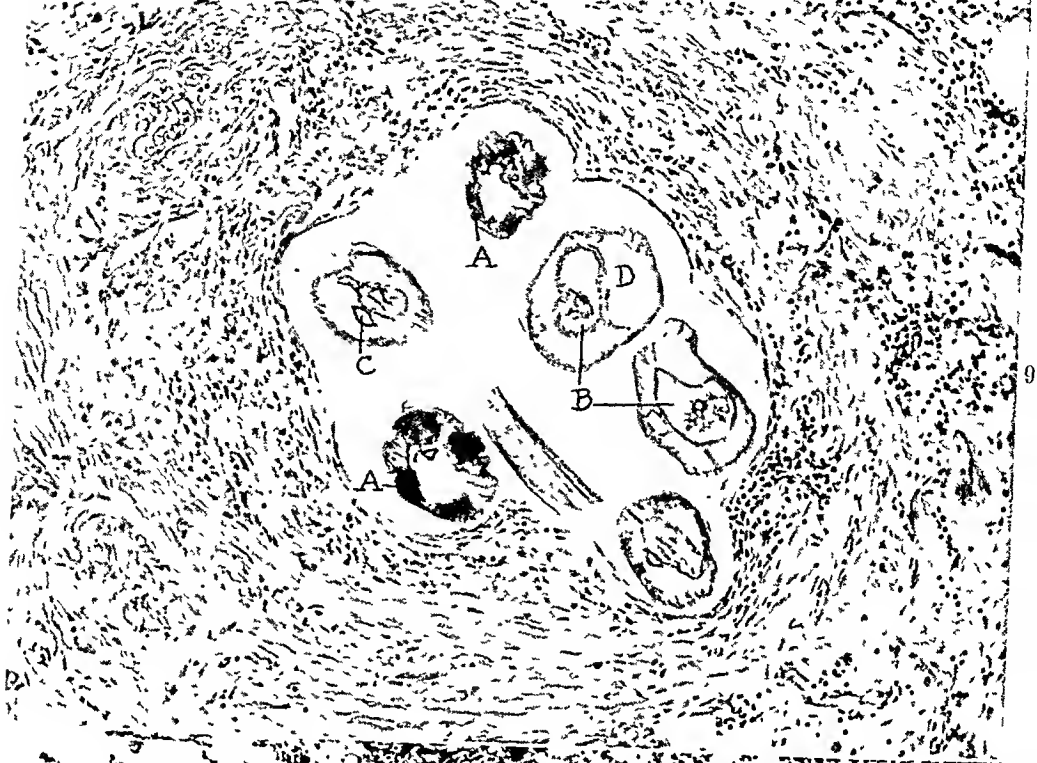
Case 3 was of exceptional interest because of the presence of acute inflammatory lesions due presumably to microfilariae There was acute thromboangitis and diffuse inflammation of all tissues characterized by marked edema, and exudation of great numbers of polymorphonuclear eosinophils, plasma cells, lymphocytes and neutrophils Macrophages were numerous and occasional giant cells of foreign body type were present One of these had partly phagocytosed a microfilaria (Fig 17) Another microfilaria was surrounded by a peculiar amorphous precipitate which stained intensely with eosin (Figs 18 and 19)

Testis

Material from the testis was available in Case 1 Normal pattern was preserved and the tubules were lined by apparently healthy cells showing active spermatogenesis Numerous well preserved spermatozoa were found in the lumens of the tubules The interstitial tissue was normal As far as could be determined pathologically the testis had not been adversely affected.

Lymph Nodes

Lymph node biopsies of 57 patients, all of whom had a history of exposure to filariasis, were available for study Eight of them contained adult worms,

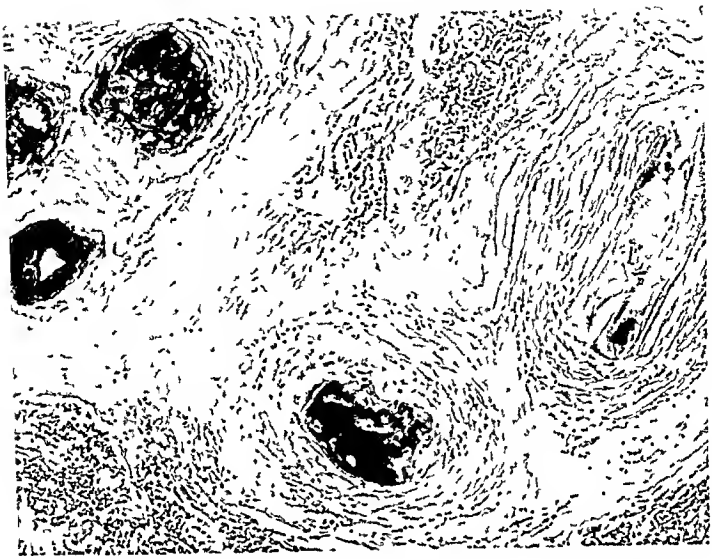


9

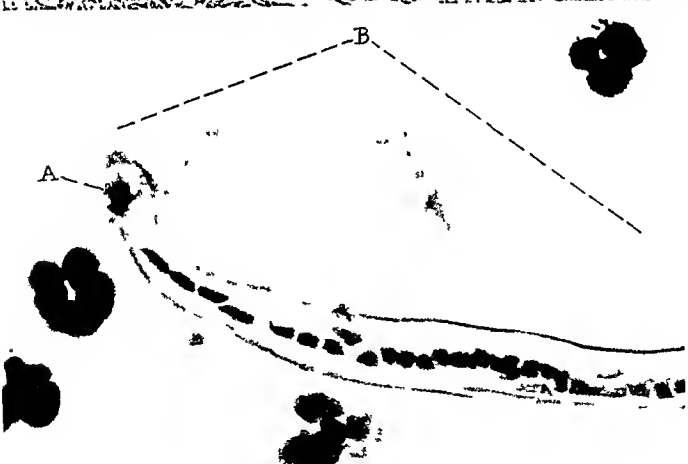
10

FIG. 9. Case 1—Accession 86686. Male Puerto Rican, 18 years old, with long-standing infection. Adult filarial worms in a lymph vessel of the spermatic cord. The lumen of the vessel is dilated and the wall thickened by hyperplasia of muscularis, edema and cellular exudate. Vascularization has also occurred. Some of the worms show hyaline degeneration of the cuticle A. The uteri are empty B. C is the esophagus and D the schistocele. Figures 29 and 33 are also from this case. H & E ×173.

FIG. 10. Case 4—Accession 96815. Male Chinese, 22 years old, with long-standing infection. A degenerating, pregnant female worm was found in a lymph vessel in the spermatic cord. A thrombus of coagulated lymph and lymphocytes has formed around the parasite. The wall of the vessel is inflamed and there is hyperplasia of muscularis. Figures 13 and 15 show microfilariae which were found in blood vessels and tissues. H & E ×175.



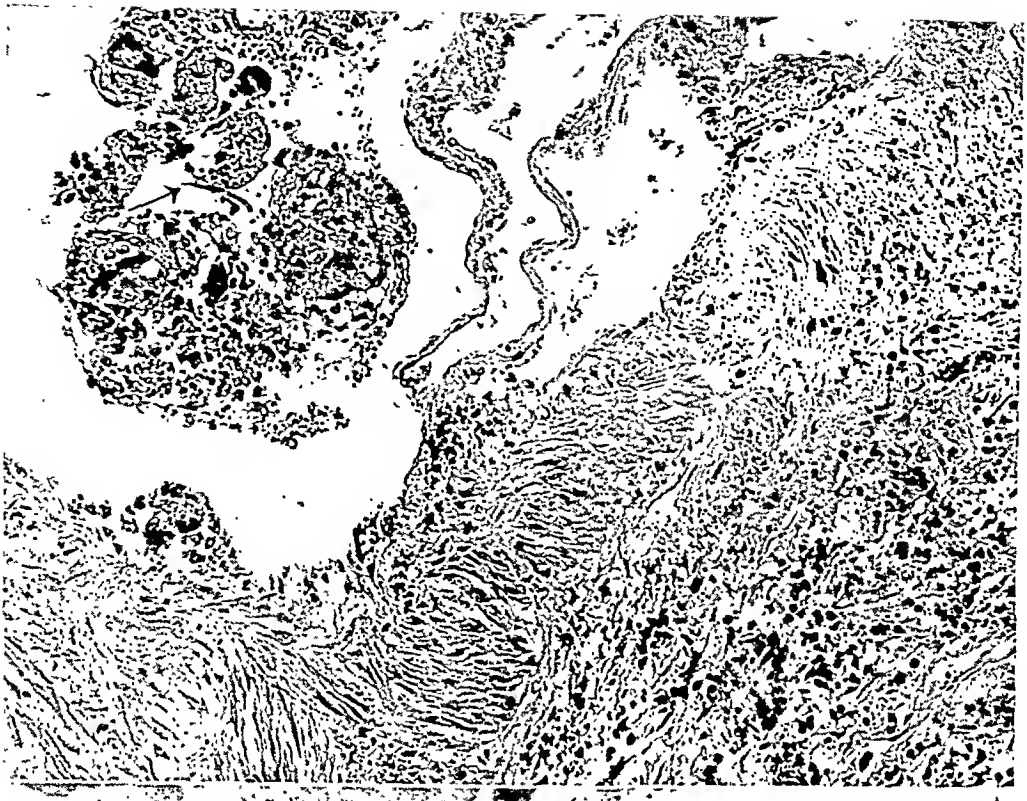
11



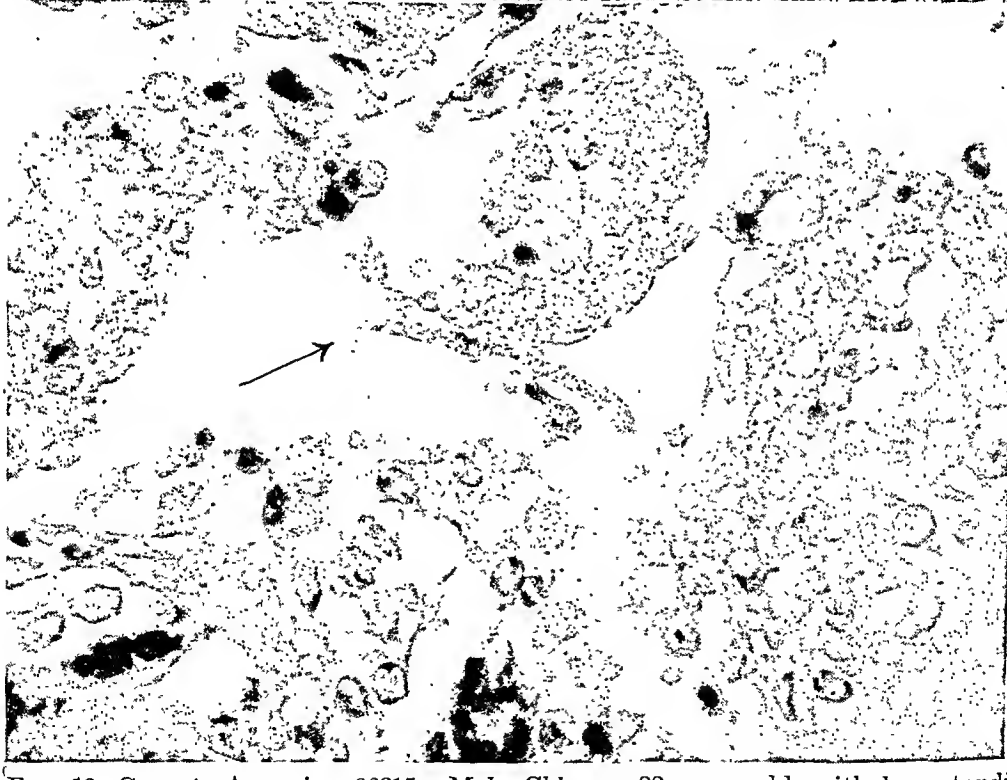
1

FIG 11 Case 2—Accession 101611 Calcification and localization of adult worms in spermatic cord of a male Puerto Rican, 37 years old, who had symptoms for about 30 years Remains of the cuticle and uterus can be seen in some of the cross sections H & E ×117

FIG 12 Microfilaria bancrofti, non periodic variety, in peripheral blood of a native of Samoa showing the absence of nuclei in the tip of the tail, A B is the sheath H & E ×2100.



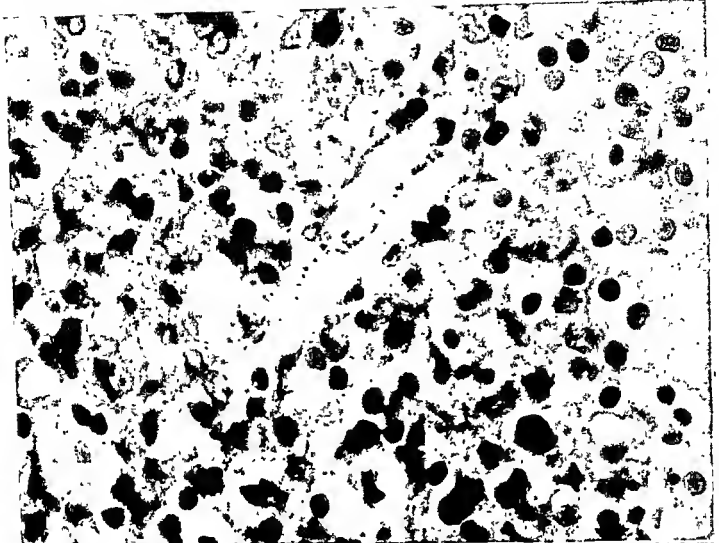
13



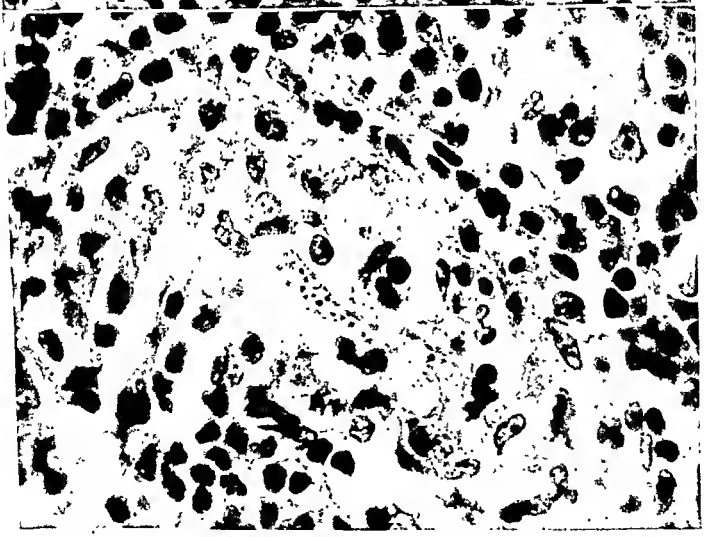
14

Fig. 13. Case 4—Accession 96815. Male Chinese, 22 years old, with long-standing nfection. A microfilaria is enmeshed in a thrombus in an inflamed lymph vessel. Notice ıow inconspicuous the parasite is with the 16 mm. lens. Proliferation of lining cells, ıyperplasia of muscularis, and exudate are present in the vessel wall. Figure 10 shows the ıdult worm in this case and Figure 15 microfilariae in the tissues. H & E ×200.

Fig. 14. Accession 96815. High power view of Figure 13 to show microfilaria and hyperplastic lining cells cast off into the lumen. H & E ×750.



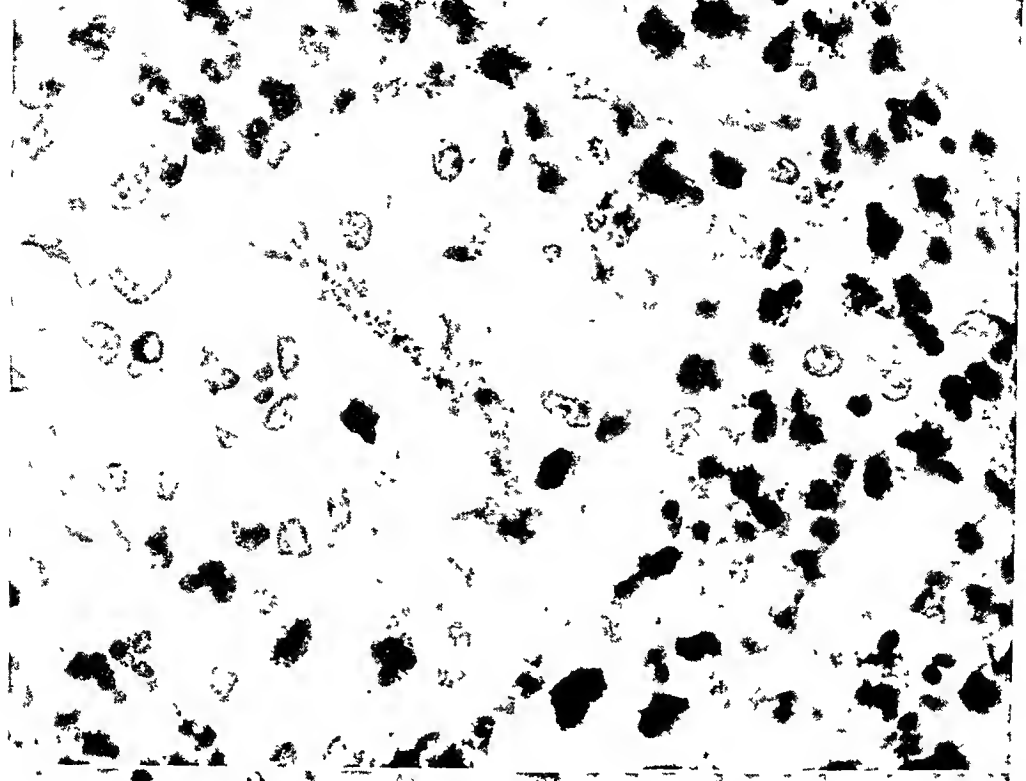
15

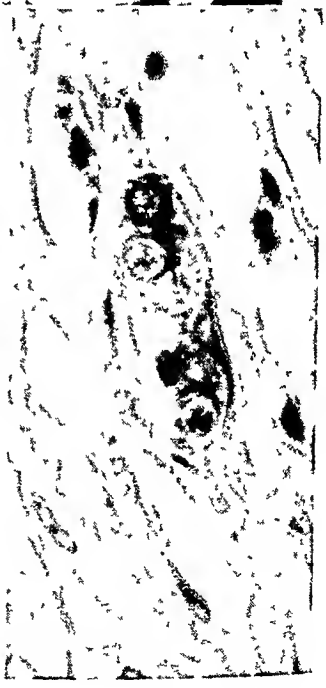


16

Fig. 15. Case 4—Accession 96815. Male Chinese, 22 years old, with long-standing infection. Longitudinal segment of microfilaria in a lymph node. Figures 10 and 13 show the adult worm in a lymphatic and microfilariae in a blood vessel in this case. H & E ×990.

Fig. 16. Case 57—Accession 144274. Tangential segment of microfilaria in an inguinal lymph node of a male Puerto Rican, 37 years old, with long-standing infection. There is no inflammation. Figure 26 shows tissue changes which were present elsewhere. H & E ×1250.





18 19 20

FIG. 17. Case 3—Accession 110147. Phagocytosis of a microfilaria by a giant cell. There is marked inflammation of surrounding tissues with large numbers of eosinophils. Nodule from the spermatic cord of a white soldier, 31 years old, infected in the South Pacific in 1944. H & E ×820.

FIG. 18. Case 3—Accession 110147. Soldier, 31 years old, infected in 1944 in the South Pacific. Microfilaria surrounded by acidophilic precipitate in an inflamed nodule in the spermatic cord. Compare this with Figure 4 where the precipitate is basophilic. H & E ×700.

FIG. 19. Case 3—Accession 110147. Two other microfilariae surrounded by acidophilic precipitate in the same case as Figure 18. H & E ×800.

FIG. 20. Accession 100815. Nodule from scalp of a patient with onchocerciasis showing microfilariae surrounded by acidophilic precipitate. Since microfilariae of O. volvulus have no sheath, the precipitate is not due to swelling of the sheath. H & E ×810.

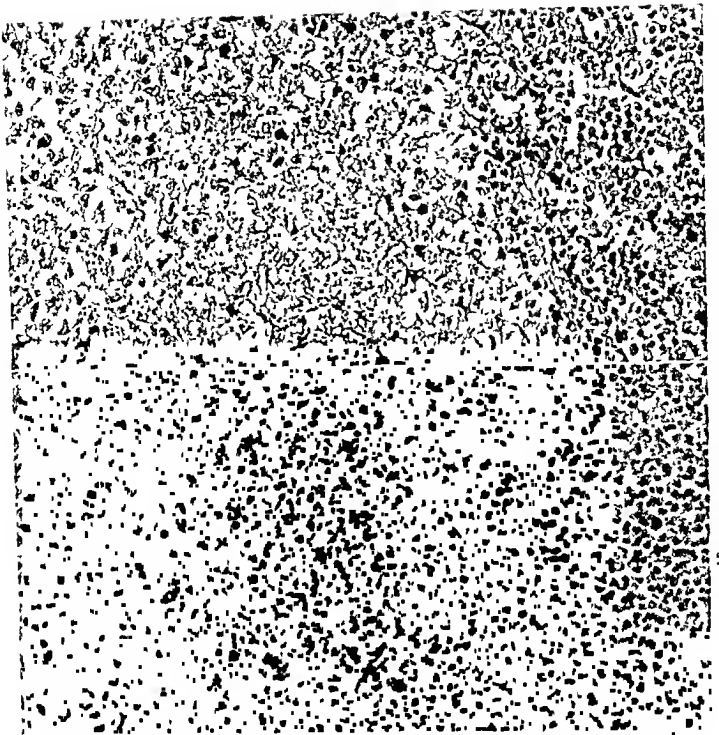


Fig. 21. Case 19—Accession 121066. Hyperplasia of littoral cells in the subcapsular [illegible] of eosinophils

Fig. 23. Case 23—Ac[illegible] [illegible]nical filariasis. Thickening of the subcapsular lymphatic sinus of an inguinal lymph node. There was also follicular hyperplasia. See Figure 28 for other changes in this node. H & E ×140.

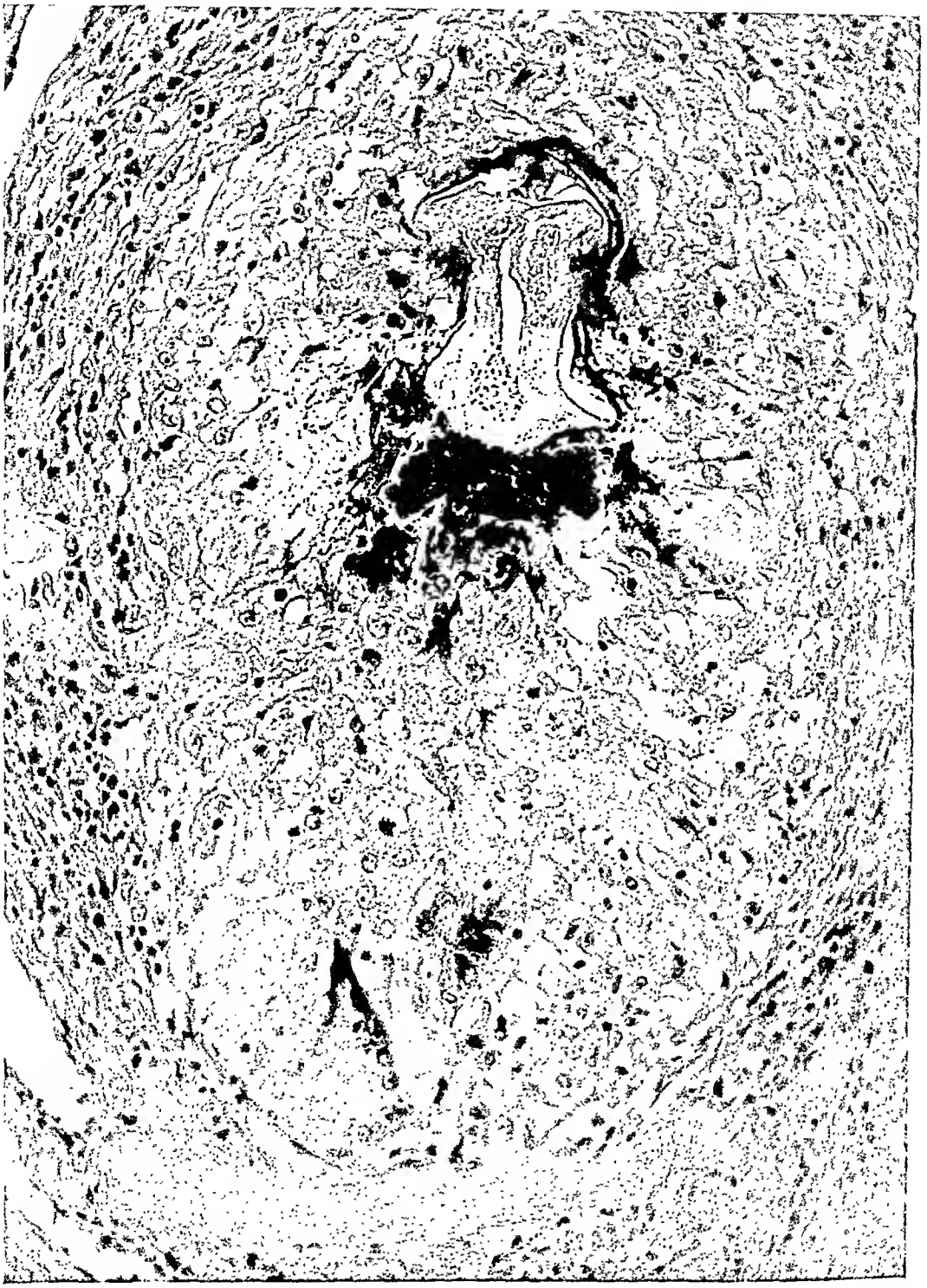


FIG. 24. Higher magnification of Figure 3 to show littoral cells and macrophages. Giant cells are present and have phagocytosed debris including portions of the eosinophilic precipitate. H & E ×280.

and two others microfilariae which could be identified as *W. bancrofti* with a reasonable degree of certainty. Twenty-three showed histologic changes which

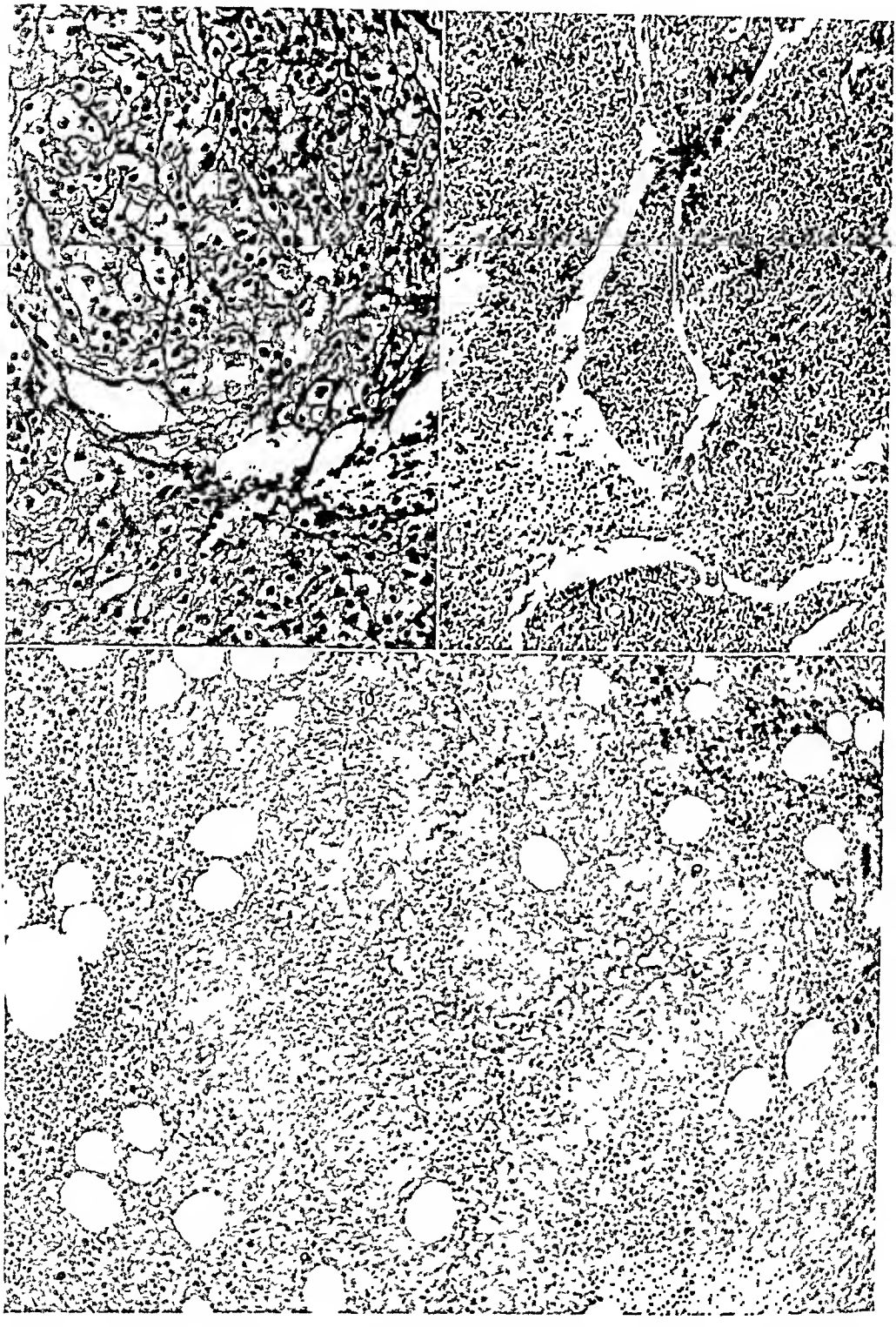
were consistent with the diagnosis of filariasis, and 24 showed no specific lesions attributable to the disease.

Lymph Nodes with Worms. The 10 lymph nodes which contained *W. bancrofti* were obtained from patients of whom 4 were infected in Wallis Island (French Samoa), 1 in Samoa, 1 in New Guinea, 2 in Puerto Rico and 1 in China. In the remaining case the place of infection was not mentioned. Except for the patients infected in Puerto Rico and China, who probably had life-long infections, the biopsies were obtained within 18 months of the first possible exposure, and usually within a few months of onset of symptoms. It is reasonable to assume that the infecting parasites were *W. bancrofti*, nonperiodic variety, (the infections in the Puerto Ricans were probably of the periodic variety) because of the geographic locations where these men were infected (Figs. 7 and 12). In the case of the Chinese patient the possibility of infection with *W. malayi* could not be excluded. Microfilariae were discovered in the blood of one Puerto Rican patient (Case 10), but in no others. Two of the biopsies showed microfilariae and 8 adult parasites. The Puerto Rican and Chinese patients had necrotic and partially calcified adult worms, whereas apparently living, as well as degenerating and dead worms were found in the other biopsies.

Typical changes in nodes which were infected with adult worms consisted of marked hyperplasia of cells of the reticuloendothelial system, tissue eosinophilia, and nodule formation. Macrophages were numerous and moderate numbers of foreign body type giant cells were present (Figs. 3 and 24). Nodules were found chiefly around adult parasites but occasionally occurred around microfilariae or even in the absence of parasites (Fig. 8). In some instances necrosis was absent, but usually it was extensive with precipitation of variable amounts of intensely acidophilic material (Figs. 1, 3, and 24). The necrotic tissue was surrounded by a border of macrophages arranged in palisade fashion. The edges of this border were often serpiginous (Figs. 1, 8, 27). Reticular fibers were increased moderately in size and greatly in number (Fig. 25). Eosinophils, plasma cells, lymphocytes and neutrophils were present throughout the granulomas, but were especially numerous at the edges. In older lesions where the worms were dead, or had been present for a long time, macrophages and exudative cells were less conspicuous, and there were concentrically arranged layers of dense acellular collagen (Fig. 11). Characteristically both young and old nodules were avascular. In other portions of the affected nodes a frequent finding was marked hyperplasia of the littoral cells of lymphatic sinuses (Fig. 21) which often resulted in tongue-like processes which projected into the sinuses (Figs. 3, 26). Tissue eosinophilia was common (Fig. 2), and at times the eosinophils were so numerous and so tightly packed that necrosis occurred, the so-called "eosinophilic abscesses" (Fig. 22).

The lesions just described were found in the superficial lymph nodes of the arm, axilla and groin. In one patient (Case 11) a retroperitoneal lymph node was available for study. This patient was a male Chinese, 21 years old, with long-standing infection which he probably had acquired in China. The changes

25 26

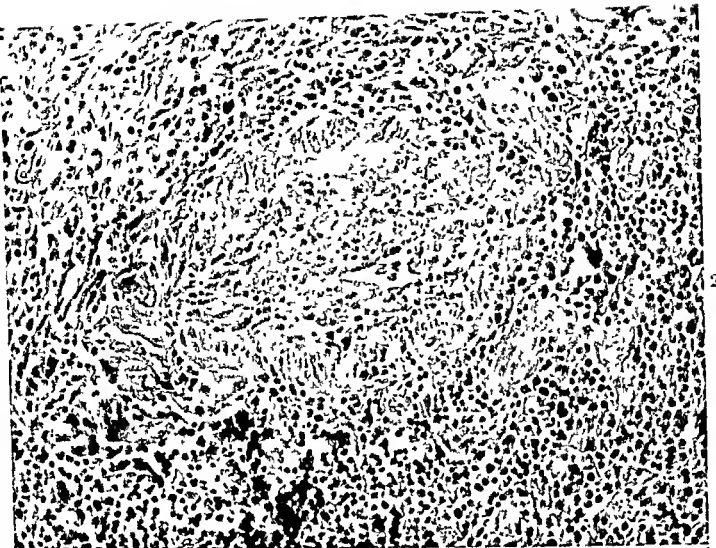


27

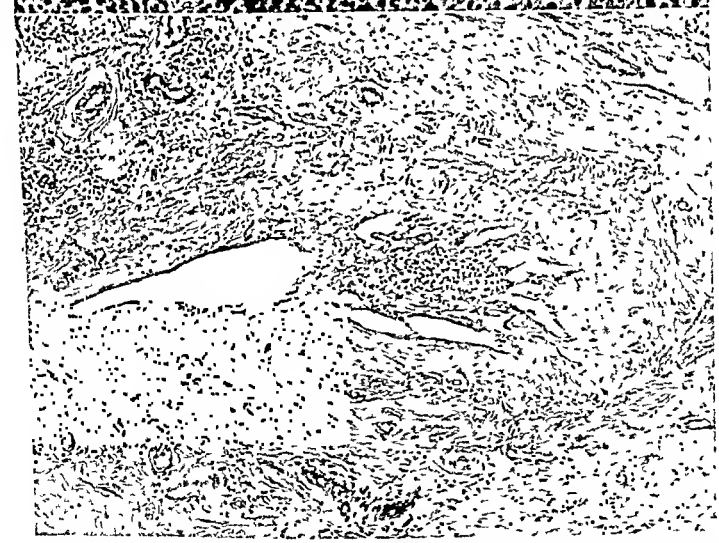
FIG. 25. Case 5. Soldier, infected on Wallis Island in 1942. Increase in silver staining reticular fibers and littoral cells in an epitrochlear lymph node which contained adult W. bancrofti. Foot's silver stain. ×250.

FIG. 26. Case 57—Accession 144274. Male Puerto Rican, 36 years old, with long-standing infection. Hyperplasia of littoral cells with finger-like projections into the medullary sinuses of an inguinal lymph node. Figure 16 shows the microfilariae discovered in the tissues. H & E ×130.

FIG. 27. Case 9—Accession 110940. Edema, exudation of eosinophiles and increase of macrophages in tissues at the hilum of a lymph node which contained adult parasites. The patient was a white soldier, 29 years old, who was infected in Samoa in 1944.



28



29

FIG 28. Case 23—Accession 102539. Negro soldier, 23 years old, with clinical filariasis. ls with obstruction of lumen of a small lymph vessel. See also

ion 86686. Villous hyperplasia of littoral cells in a lymph vessel lema and muscular hyperplasia are evident as well as inflamma- ... Figures 9 and 33 are also from this case. H & E ×140.

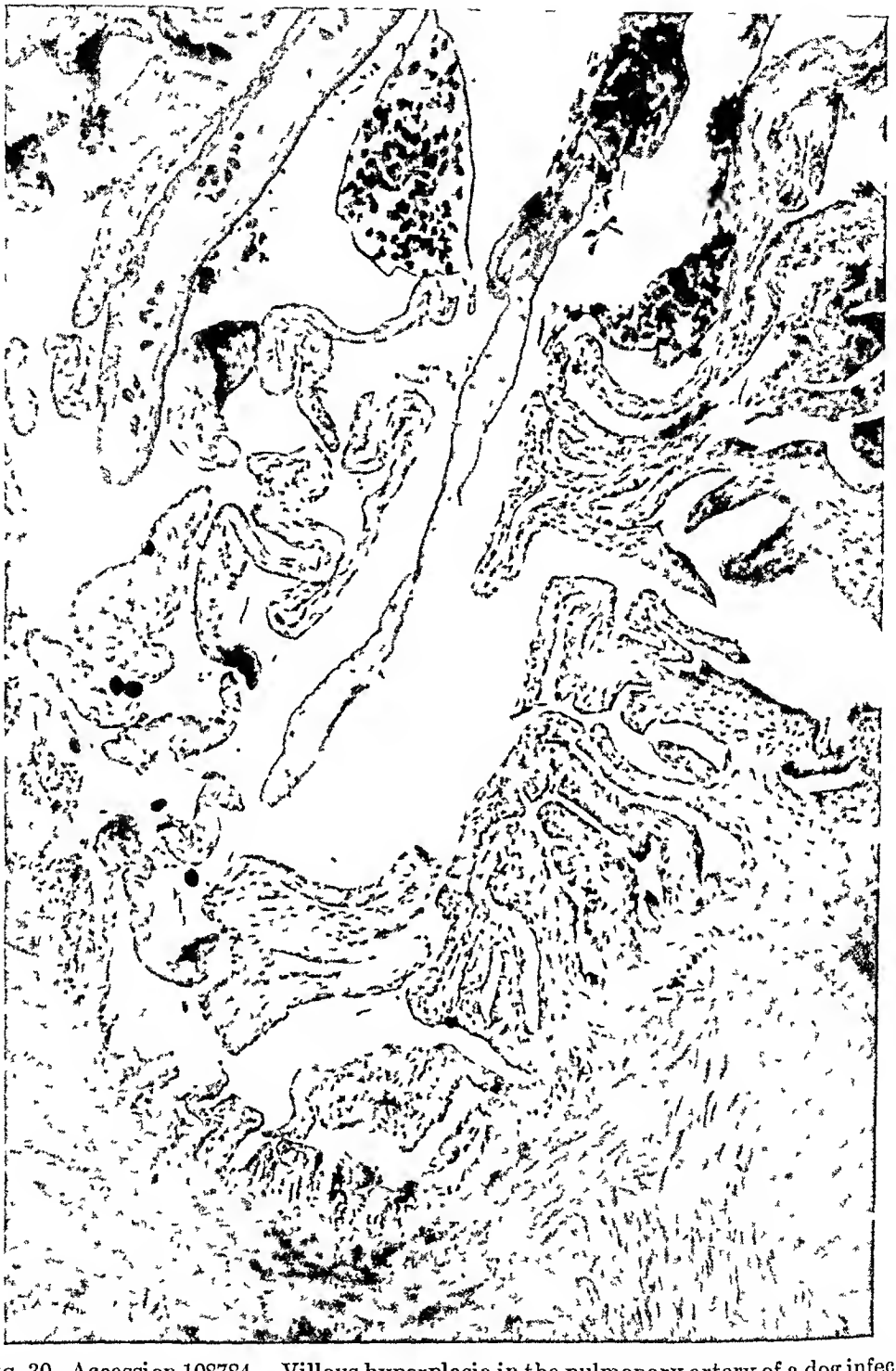
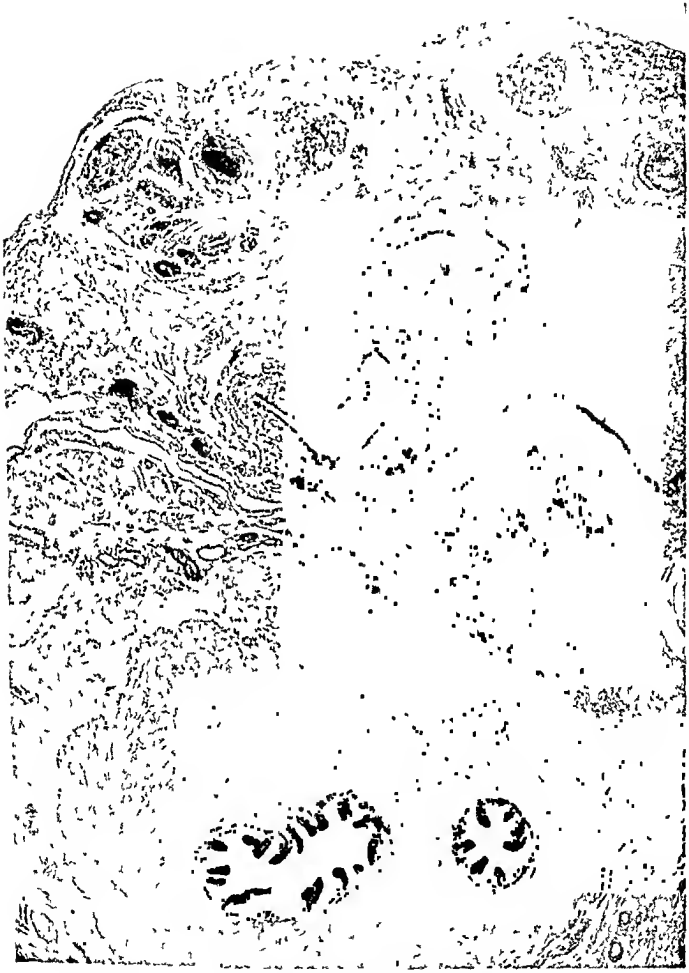


FIG. 30. Accession 108784. Villous hyperplasia in the pulmonary artery of a dog infected with Dirofilaria immitis. Hyperplasia is commonly produced by many varieties of filarial worms in either lymphatic or blood vessels.

in this biopsy are identical with those in the other patients (Figs. 3, 24). This is one of the very few biopsies from deeply situated lymph nodes which have been described.



148685 Spermatic cord from a soldier, 27 years old, with lymph vessels are involved but not the vas deferens Acute ...nces is an acute lymphangitis of the spermatic cord H & E

×20

Two of the biopsies contained microfilariae, although no adult parasites were found. In such cases the lesions were similar to those associated with adult worms, but there were some points of difference. Necrosis was not observed

otherwise healthy young men. There was accurate information about the duration of the disease and there were no complicating factors such as reinfection and secondary bacterial infections, which made it difficult to interpret the findings of earlier workers (29, 2, 6, 36) who studied natives in endemic areas. As a result of the war experience clear evidence has accumulated that early filariasis is due solely to *W. bancrofti* and is not caused by bacteria or conditioned by their presence. Even after many months bacteria have not entered into the picture. Much other evidence indicates that *W. bancrofti* is the etiologic agent, such as the demonstration of adult and larval parasites accompanied by significant lesions in involved tissues, the results of intradermal testing, and the clinical manifestations of the disease. These facts disprove the belief in a bacterial etiology. This is not to say, of course, that in natives or in late states of the disease such as elephantiasis bacteria may not play a part.

Accurate knowledge of the incubation period of filariasis has been obtained. Patients have contracted the disease and *W. bancrofti* have been discovered in lymph node biopsies with'n 3 months of the first possible exposure. In other patients clinical evidences of filariasis have developed within one month although worms could not be found. The skin test when made with suitable antigens and adequate controls has been a useful diagnostic procedure. Microfilariae were almost constantly absent from the blood stream so that failure to find them should not exclude the diagnosis. No satisfactory explanation has been given of this fact. This is not a new observation, since many earlier students of the disease (6, 29, 36) were entirely familiar with it.

Study of the literature of filariasis shows that the syndrome which was seen in our troops had been described previously in both natives and whites (29, 2, 36, 6). Usually the disease was called by the Samoan word "mumu". When the clinical descriptions of these older workers are compared with those of the Army and Navy Medical Officers there is little doubt that our Armed Forces had "mumu". The belief of the older authors, which they were unable to prove, that mumu was an early stage of filariasis, has thus received confirmation. This form of the disease is apparently different from filariasis as it is seen in natives in India where mumu is said to be unusual (35).

The results of this study are in agreement with previously published descriptions of the pathology of early filariasis in American Armed Forces. The results are also in general agreement with those of the older investigators, notably O'Connor, and O'Connor and Hulse, who studied the disease in natives in the Western Pacific and in Puerto Rico. This work has been critically reviewed by Temkin, and the reader is referred to his article for details. The only essential difference is that O'Connor believed only dying or dead adult worms elicit tissue reactions, whereas the experience in World War II suggests that living worms may also cause lesions. Van der Sar and Hartz described lesions which they attribute to the presence of microfilariae and this has been confirmed by study of the material at the Army Institute of Pathology. Data have also been obtained on pathologic lesions in the genital organs. Of importance is the

demonstration that filarial funiculitis, epididymitis and orchitis are due to acute inflammation of the lymph vessels in these organs. Thus the lesions correspond to filarial lymphangitis of the extremities. With the exception of one case in which a biopsy was taken from a retroperitoneal lymph node, and one reported autopsy (32), there was no material available for study of lesions produced in the deep lymph vessels or other organs. The material that has been studied indicates that similar changes occur in both superficially and deeply situated lymph nodes.

It is interesting to make a comparison of the tissue reactions associated with adult worms, and with microfilariae. In the former there is precipitation of strongly acidophilic material about the worms with necrosis of tissues, exudation of eosinophils, plasma cells and lymphocytes, and proliferation of macrophages and reticular fibers. In the latter there is no necrosis and the precipitate around the microfilariae, when it occurs, is amphoteric. Edema is conspicuous and the exudate is comprised chiefly of eosinophils. Macrophages and giant cells, although present, are not numerous and there is only slight reticular hyperplasia. The nature of the precipitate which occurs about both adult worms and larvae is not known, but it seems likely that it is a protein and that it may result from an antigen-antibody reaction.

No discussion of early filariasis would be complete without consideration of the part played by hypersensitivity. Many clinical manifestations of early filariasis such as blotchy redness of the skin, absence of severe constitutional symptoms, blood eosinophilia, and rapid appearance and disappearance of symptoms, are suggestive of hypersensitivity. During attacks of acute lymphangitis in one extremity there is not infrequently enlargement of lymph nodes in distant parts of the body such as the neck, groin or opposite extremity. The high incidence of positive skin tests, desensitization, passive transfer experiments, and reproduction of some of the characteristic signs and symptoms by intradermal injection of a suitable antigen, can all be explained on this basis. But, pathological proof of this theory is not possible because of the fact that there are no tissue changes which are specific of hypersensitivity. Nevertheless, the great edema, exudation of eosinophils, necrosis, and precipitation of acidophilic or basophilic material around the parasites, are at least consistent with this explanation. Marked increase in macrophages is also known to occur in other diseases in which hypersensitivity is thought to play a part, notably tuberculosis and rheumatic fever. Such lesions were often much more severe in filariasis than would be expected from the clinical symptoms of the patients or from naked-eye examination of the tissues. Available evidence suggests that this is an anaphylactic type of hypersensitivity. There is marked tissue eosinophilia and endothelial damage and necrosis of tissues pathologically, while clinically the hypersensitivity can be passively transferred and an immediate skin reaction is obtained with *D. immitis* antigen. However, the occurrence of delayed reactions to skin testing and the failure to demonstrate precipitins in circulating blood are more often found in the tuberculin type than in the anaphylactic type of hypersensitivity. It may be concluded, therefore, that both clinical and patho-

logic evidence support the theory that the symptoms and signs of early filariasis in American Armed Forces were due in part to the development of hypersensitivity by the host to *W. bancrofti.*

To the best of the author's knowledge, similar cases of early filariasis have not so far been reported by our allies. While the author was in Brisbane, Dr. E. H. Derrick showed him 2 lymph node biopsies from Australian troops who had been waging guerrilla warfare in Dutch Timor. Although no parasites were present, the lesions suggested a diagnosis of filariasis.

BIBLIOGRAPHY

1. Augustine, D. L.: Filariasis. New York State J. Med., **45**: 495, 1945.
2. Bahr, P. H.: Filariasis and elephantiasis in Fiji. Research Memoirs of the London School of Tropical Medicine, Vol. I, 1912, London.
3. Bozicevich, J., and Hutter, A. M.: Intradermal and serological tests with Dirofilaria immitis antigen in cases of human filariasis. Am. J. Trop. Med., **24**: 203, 1944.
4. Bulletin U. S. Army Medical Department, **4**: 294, 1945.
5. Burhans, R. A., Camp, J. D., Butt, H. R., and Cragg, R. W.: Lymphangitis of suspected filarial origin; preliminary report concerning its treatment. U. S. Nav. M. Bull., **42**: 336, 1944.
6. Buxton, P. A.: Researches in Polynesia and Melanesia, an account of investigations in Samoa, Tonga, the Ellice Group, and the New Hebrides, in 1924, 1925. Parts V–VII, The London School of Hygiene and Tropical Medicine, London, 1928.
7. Byrd, E. E., St. Amant, L. S., and Bromberg, L.: Studies on filariasis in Samoan Area. U. S. Nav. M. Bull., **44**: 1, 1945.
8. Coggeshall, L. T.: Problems of filariasis. South. M. J., **38**: 186, 1945.
9. Coggeshall, L. T.: Malaria and filariasis in the returning serviceman. Am. J. Trop. Med., **25**: 177, 1945.
10. Coggeshall, L. T.: Lymphadenopathy and filariasis. Bull. U. S. Army Med. Dept., **5**: 250, 1946.
11. Culbertson, J. T., Rose, H. M., and Demarest, C. R.: Filariasis bancrofti; its diagnosis by immunologic tests with antigen derived from Litomosoides carinii. Am. J. Hyg., **39**: 156, 1944.
12. Damin, G. J., and Weller, T. H.: Heterophile agglutinins and cold autohemagglutinins in schistosomiasis, filariasis, malaria, and leprosy. Am. J. Trop. Med., **25**: 97, 1945.
13. Dhayagude, R. G., and Amin, B. M.: Microfilarial granulomata of the spleen. Am. J. Path., **18**: 351, 1942.
14. Dickson, J. G., Huntington, R. W. Jr., and Eichold, S.: Filariasis in defense force, Samoan group; preliminary report. U. S. Nav. M. Bull., **41**: 1240, 1943.
15. Englehorn, T. D., and Wellman, W. E.: Filariasis in soldiers on an island in South Pacific. Am. J. M. Sc., **209**: 141, 1945.
16. Flynn, P. D.: Filariasis suspects; review of cases admitted. U. S. Nav. M. Bull., **42**: 1075, 1944.
17. Fogel, R. H., and Huntington, R. W. Jr.: Genital manifestations of early filariasis. U. S. Nav. M. Bull., **43**:263, 1944.
18. Glauser, F.: Filariasis in returning marines. U. S. Nav. M. Bull., **44**: 21, 1945.
19. Goodman, A. A., Weinberger, E. M., Lippincott, S. W., Marble, A., and Wright, W. H.: Studies of filariasis in soldiers evacuated from the South Pacific. Ann. Int. Med., **23**: 832, 1945.
20. Hartz, P. H.: Contribution to histopathology of filariasis. Am. J. Clin. Path., **14**: 34, 1944.
21. Haviland, J. W.: Recent experiences with filariasis. Northwest Med., **43**: 371, 1944.
22. Hayman, J. M.: Personal communication.

23. Hodoe, I. G., Denhoff, E., and Vanderveer, J. V.: Early filariasis (Bancrofti) in American soldiers. Am. J. M. Sc., 210: 207, 1945.
24. Huntinoton, R. W. Jr., Fogel, R. H., Eichold, A., and Dickson, J. G.: Filariasis among American troops in a South Pacific Island group. Yale J. Biol. & Med., 16: 529, 1944.
25. Huntinoton, R. W. Jr.: Skin reactions to Dirofilaria immitis extract. U. S. Nav. M. Bull., 44: 707, 1945.
26. Johnson, P. A. G.: Filariasis; clinical findings in 189 cases. U. S. Nav. M. Bull., 43: 950, 1944.
27. King, B. G.: Early filariasis diagnosis and clinical findings; report of 268 cases in American troops. Am. J. Trop. Med., 24: 285, 1944.
28. Lane, C.: Bancroftian filariasis and the reticuloendothelial system. Tr. Roy. Soc. Trop. Med. & Hyg., 31: 61, 1937.
29. Leber, A., ann v. Prowazek, S.: Bericht übermedizinische Beobachtungen auf Savaii and Manono (Samoa). Arch. f. Schiffs- u. Tropen-Hyg., 15: 409, 1911.
30. Leene, W. E., ann Josey, A. I.: The early diagnosis of filariasis and certain suggestions relative to cause of symptoms. Ann. Int. Med., 23: 816, 1945.
31. Lowman, E. W.: Incidence of filariasis in children. U. S. Nav. M. Bull., 42: 341, 1944.
32. Michael, P.: Filariasis among Navy and Marine personnel; report on laboratory investigations. U. S. Nav. M. Bull., 42: 1059, 1944.
33. Michael, P.: Filariasis; histopathologic study. U. S. Nav. M. Bull., 45: 225, 1945.
35. Napier, L. E.: Filariasis due to Wuchereria bancrofti. Medicine, 23: 149, 1944.
36. O'Connor, F. W.: Some results of medical researches in the Western Pacific. Tr. Roy. Soc. Trop. Med. & Hyg., 16: 28, 1922.
37. O'Connor, F. W., and Hulse, C. R.: Studies in fi riasis. Puerto Rico J. Pub. Health & Trop. Med., 11: 167, 1935. la
38. Oliver-Gonzalez, J., ann Bercovitz, Z. T.: Precip tin reactions with antigen prepared from microfilariae of Wuchereria bancrofti; (preliminary report). Am. J. Trop Med., 24: 315, 1944.
39. Oliver-Gonzalez, J., ann Morales, F. H.: Common antigens among filarial and other nematode parasites of man. J. Infect. Dis., 77: 92, 1945.
40. Pastennack, J. G.: Filarial epididymofuniculitis. Arch. Path., 35: 414, 1943.
41. Rifkin, H., and Thompson, K. J.: Structural changes in early filariasis. Arch. Path., 40: 220, 1945.
42. Rome, H. P., ann Fogel, R. H.: Psychosomatic manifestations of filariasis. J. A. M. A., 123: 944, 1943.
43. Smith, F. R. Jr.: Filariasis; a study of 737 patients so diagnosed. U. S. Nav. M. Bull., 44: 719, 1945.
44. Temkin, O.: A report on the medicinal treatment of filariasis bancrofti. Nat. Res. Council, Div. Med. Sc., Washington, Sept., 1945.
45. Thompson, K. J., Rifkin, H., ann Zarrow, M.: Early filariasis. J. A. M. A., 129: 1074, 1945.
46. van der Sar, A., ann Hartz, P. H.: The syndrome, tropical eosinophilia and microfilaria. Am. J. Trop. Med., 25: 83, 1945.
47. Wartman, W. B.: Lesions of the lymphatic system in early filariasis. Am. J. Trop. Med., 24: 299, 1944.
48. Wartman, W. B., ann King, B. G.: Early filariasis in American soldiers. Bull. U. S. Army M. Dept., 75: 45, 1944.
49. Zarrow, M., ann Rifkin, H.: Observations on the specificity and clinical use of Dirofilaria immitis antigen in the diagnosis of human filariasis (Wuchereria bancrofti). Am. J. M. Sc., 211: 97, 1946.
50. Zuckerman, S. S., and Hibbard, J. S.: Clinicopathologic study of early filariasis with lymph node biopsies. U. S. Nav. M. Bull., 44: 27, 1945.

Additional Bibliography

51. Behm, A. W., and Hayman, J. M.: The course of filariasis after removal from an endemic area. Am. J. M. Sc., **211**: 385, 1946.
52. Brown, T. McP., Bethea, W. R. Jr., and Stifler, W. C. Jr.: Early filariasis. Bull. Johns Hopkins Hosp. **78**: 126, 1946.
53. Saphir, W.: Filariasis. J. A. M. A., **128**: 1142, 1945.
54. Zeligs, M. A.: Psychosomatic aspects of filariasis. J. A. M. A., **128**: 1139, 1945.
55. Coggeshall, L. T.: Filariasis in the serviceman; retrospect and prospect. J. A. M. A., **131**: 8, 1946.

THE NERVOUS SYSTEM IN TROPICAL DISEASE

A Clinical Review[1]

W. S. CHALGREN, M.D. and A. B. BAKER, M.D.

From the Division of Neurology, The Medical School, University of Minnesota, Minneapolis

The present widespread interest in tropical diseases is a direct result of the recent extensive military operations in tropical and subtropical countries. While many of these diseases are actually world-wide in their distribution, they are more prevalent and more serious in the warmer regions of the earth where health and sanitation practices are poorly effective. A great many reports and publications dealing with various aspects of tropical diseases have appeared in the past several years. Many of them describe the clinical manifestations of the infection, but they often tend to overlook or to minimize symptoms suggesting a nervous system involvement. In this paper an attempt will be made to review the symptomology of the diseases commonly regarded as tropical, with an emphasis on the neuropsychiatric manifestations and complications. Brief mention will be made of the general clinical and epidemiological characteristics of the disease, and of the principle pathological changes found in the nervous system. It has been found that in practically all of the diseases discussed there was involvement of an encephalitic nature. These changes have been reviewed in a previous paper (Chalgren and Baker (1)).

YELLOW FEVER

Yellow fever is an acute infectious jaundice caused by a virus which is transmitted from man to man by the mosquito, Aedes aegypti. It occurs in endemic foci as jungle yellow fever in vast areas of tropical South America and Africa, and in epidemic form in various urban communities in equatorial Africa and tropical South and Central America. After an incubation period of from three to seven days, the onset of the disease is usually abrupt, with slight chills and fever, headache, muscle pains, nervousness and anxiety. These symptoms are followed in a day or two by albuminuria, oliguria, increasing fever, nausea, vomiting and severe prostration. Jaundice appears on the fourth or fifth day accompanied by bleeding from the gums and hemorrhages in the stomach and intestine. Death usually occurs from the sixth to the ninth day preceded by delirium, prostration and coma. The mortality ratio in epidemics has been reported from 5 to 10 per cent up to 80 per cent.

The essential pathological lesions in yellow fever are found in the liver and are characterized by mid-zonal necrosis and fatty degeneration. Less striking changes are noted in the spleen, kidneys, heart, lungs and gastro-intestinal tract. In the brain a definite encephalitis has been demonstrated. Jacob, Fialho and Villela (2) observed a mild meningeal infiltration, marked fatty degeneration of

[1] This study was aided by a grant from the Research Fund of the Graduate School of the University of Minnesota.

cerebral ganglion cells and of endothelial cells, perivascular gliosis, and focal collections of glial cells. Stevenson (3) emphasized the findings of perivascular hemorrhages, and Nicolau, Mathis and Baffet (4) noted oxyphilic inclusion bodies in addition to the above findings. Encephalitis has also been demonstrated in experimental animals (Goodpasture (5), Lloyd and Penna (6), Findlay and Stern (7)). A modified neurotropic strain of the virus has been used for vaccination and has resulted in the development of an occasional clinical case of encephalitis (Sorel (8), Fox et al. (9)).

Nervous system involvement is suggested clinically by a number of symptoms which develop during the course of the infection. Headache is usually very pronounced even at the onset, and the prostration is out of proportion to the other evidences of the illness. Jungman (10) described a case in which the weakness was so great that it resembled a paralysis of the limbs. Hoffmann (11) found severe headache to be the beginning symptom in two-thirds of his cases. Pains and tenderness in the back and limbs were usually present. Berry and Kitchen (12) described two cases in which generalized hyperesthesias were prominent. Numerous authors have reported scattered cranial nerve involvement (hiccough) (Aitken, et al. (13)), paralysis of vocal cords (Nicolson (14)), ptosis and facial palsy (Findlay and Stern (15)), diplopia (Ristol (16)), and transient blindness (Fernandez (17)). Stephanopoulo and Mollaret (18) described a patient who on hospitalization was prostrated and semi-comatose, with alternating periods of delirium. Tics and other muscular spasms were present and when consciousness was finally regained the patient developed a hemiplegia with aphasia. Six months later there were still evidences of the previous hemiplegia, together with a bilateral optic neuritis.

Mental symptoms, though usually mild, are by no means uncommon. Early in the course of the disease the patient may appear drowsy, but is easily aroused and often seems nervous and apprehensive. Later restlessness is evident, followed by excitement, confusion, delirium and finally coma. Hallucinations were reported by Saunders (19) and delirium tremens by Perez Aranibar (20). Le Gac (21) called attention to the extreme nervous excitement which may be seen in yellow fever patients. Hanson (22), in describing his own symptoms, noted a strange feeling of uneasiness at the outset, followed by moderate headache and later by marked soreness of the back and profound prostration. He experienced nervous manifestations of alternating excitability and depression resulting in moments of unconsciousness, delusions and weird dreams.

The cerebrospinal fluid was found by Lacorte and Villela (23) to be under increased pressure with an increase in the albumin and chlorides. In experimental animals inoculated with ordinary yellow fever a definite leucocytosis in the spinal fluid has been observed (Mollaret and Stephanopoulo (24)).

DENGUE FEVER

Dengue fever is a common virus disease occurring in both epidemic and endemic forms in subtropical and tropical countries around the world. It is prevalent in all the islands and countries of the Pacific. Several epidemics have occurred

in the United States. The disease is transmitted by the mosquito Aedes aegypti, though other mosquitoes, including Aedes albopictus (the most common oriental mosquito) may be vectors.

The clinical picture in dengue fever can be kaleidoscopic and may produce disturbances of the gastro-intestinal tract, heart, adrenals and nervous system, any one of which may dominate the picture (King (25)). After an incubation period of from 5 to 9 days, the illness develops abruptly with chills and a high temperature. There may be a mild rash, an intense headache, post orbital pain and severe backache. Pains in the limbs, joints and muscles are rarely absent and may be severe. Malaise, anorexia and nausea are common. After the third or fourth day the temperature drops to near normal for a few hours to a day or so, only to rise again producing a saddle-back fever curve. The second febrile attack is usually accompanied by an exacerbation of symptoms and often by a terminal rash. Leucopenia is a fairly constant finding. The illness terminates rapidly about the sixth day followed by a convalescence of from one to several weeks.

Involvement of the nervous system is extremely common in this disease and has been emphasized by many investigators (Apostolopoulos (26), Ghiannoulatos (27), Richardson (28), Bargy (29)). Some investigators, particularly Apostolopoulos (26) and Pamboukis (30), believe that the dengue virus is chiefly neurotropic and that the clinical manifestations are the indirect result of action by the virus upon the vegetative nervous system. In the Greek epidemic in Athens in 1928 the most marked symptoms in this disease were those of a polyneuritis, a myelitis or an encephalitis (Ghiannoulatos (27)). This author described a case of a 27 year old female who developed pain and weakness of all limbs, with complete paralysis by the 11th day. She also developed bulbar involvement, amblyopia and a mild optic neuritis. The paralysis began to improve in one month but residuals were present a year later. Photophobia, vertigo, numbness in the limbs, pareses, lethargy and convulsions have been noted (Gill (31), Ghiannoulatos (27), Richardson (28), Faver (32), Bargy (29), Simmonds (33)). The sudden development of epileptiform seizures several weeks following recovery has been described (Tsiminakis (34)). Paresthesias were reported in an epidemic among troops (Stewart (35), Kisner and Lisansky (36)). Convalescence may last two to three weeks or longer and is characterized by weakness, anorexia, asthenia, hypochondriasis and emotional instability. A definite mental depression has been emphasized by several authors (Simmonds (33), Kisner and Lisansky (36), Stewart (35)). Kaplan and Lindgren (37) noted a number of neurologic complications occurring from a day to five weeks following the acute episode. Their series included two cases each of Bell's palsy, palatine palsy, long thoracic nerve palsy, ulnar nerve palsy and peroneal nerve involvement, and one case of sciatic neuritis.

Spinal fluid examination in a case reported by Kisner and Lisansky (36) showed a lymphocytosis of 60 cells per cubic centimeter. In another case studied by Le Roy and Lindberg (38), the spinal fluid was normal but the headache was relieved instantly after lumbar puncture.

Pathological studies have been few and have shown congestion and scattered petechiae in the various organs. Catsaras (39) found swollen cortical neurons and Melissinos (40) reported degenerative, inflammatory and hemorrhagic changes within the brain tissue.

RICKETTSIAL DISEASE

The rickettsias are minute bacterium-like micro-organisms which live and multiply intracellularly in the tissues of arthropod or animal hosts. The diseases of man which are caused by rickettsias may be divided into four groups on the basis of epidemiological, pathological and immunological studies. They are the typhus fever group which is transmitted by body lice and fleas, the Rocky Mountain spotted fever group transmitted by ticks, the tsutsugamushi fever group transmitted by mites, and Q fever which may be transmitted either by ticks or by droplet infection.

With the exception of Q fever these diseases are clinically, pathogically and immunologically quite similar. They are characterized by a sudden onset, rash, fever of fairly well defined duration, various nervous and mental disturbances and prostration. The rickettsias appear to have definite neurotropic tendencies, invading the brain to produce a primary encephalitic process. The principle pathological lesions are proliferative and inflammatory changes in the smaller branches of the vascular system, most marked in the skin, heart, kidneys and brain.

Epidemic and endemic typhus fever. Epidemic typhus is caused by Rickettsia prowazeki and transmitted from man to man by the louse (Pediculus humanus). It is world wide in distribution and severe epidemics are associated with war, overcrowding and poor hygienic conditions. Endemic foci of this disease are present in the highlands of Central and South America, North Africa and parts of Central and South Africa, in southern and eastern Europe and in Asia Minor, India and China.

The incubation period is from 8 to 12 days and there may be 1 or 2 days of mild prodromal symptoms of malaise and headache, followed by an abrupt onset of chills, fever and more severe headache. The fever terminates by crisis or rapid lysis at the end of the second week. Signs of cardiac weakness are present from the onset and bronchopneumonia and gangrene of the extremities may occur. The diagnostic rash appears from the third to the seventh day, first on arms, chest and abdomen, later spreading over the entire body. Prostration is severe and fatal cases terminate in coma. The mortality rate varies from 50 to 70 per cent.

There is no question that the nervous system manifestations of typhus fever form an important part of the symptom complex. Gerhard (41) in 1837 described vertigo, blurring of vision, tinnitus, partial deafness, restlessness, somnolence, hyperesthesias, tremors, confusion, delirium and stupor. Murchison (42) in 1873 included the above symptoms and added photophobia, myalgias, paralysis, ataxia, rigidity, convulsions, insomnia, meningitis, amaurosis, and mental deterioration. Similar symptoms have been noted by other authors

(Curschmann (43), Hampeln (44), Hirschberg (45)). Devaux (46) in commenting on the epidemic in Roumania in 1919 stated, "There are few patients who do not present either during the febrile period or during convalescence some more or less grave and persistent trouble indicating central nervous system and peripheral nerve involvement." He described the neurological complications during the first week as consisting of delirium, convulsions, monoplegias and hemiplegias. During the second week the symptoms showed a bulbar localization with labio-glosso-laryngeal paralyses. Most of the neurologic symptoms occurred during convalescence and included polyneuritis, hemiplegias, cerebellar syndromes, deafness, amaurosis, emotional disturbances and mental deterioration. Rabinowitsch (47) described the nervous system symptoms in 290 cases. During the first week of the illness there occurred headache, insomnia, irritability, decreased salivary secretion, and pains in the neck and shoulders. About the 8th or 9th day there developed a stage of excitement in which hyperactivity, volubility, euphoria, sleeplessness and delirium with unsystematized delusions, hallucinations, confabulation and Witzelsucht were prominent. During this stage the abdominal reflexes were reduced, the deep tendon reflexes increased and often unequal, and pathological reflexes were present. Paresis of muscles or muscle groups was sometimes present. In the third stage, from the 9th to the 12th day the patients were physically and mentally retarded, bulbar signs were prominent, the musculature was spastic and often rigid, with Parkinsonian tremors. The mental picture resembled schizophrenia with negativism, stereotypy and catalepsy. Following this, about the 12th or 13th day or earlier in severe cases, the author described a stage of lethargy with somnolence or coma and incontinence. A fifth stage during defervescence was characterized by medullary symptoms including disturbances in the pulse and respiration and hiccough. Hearing loss and meningeal signs were noted at various times and hemorrhagic syndromes consisting of hemiplegias and aphasias were most frequent just before the crisis. Various symptoms of peripheral neuritis were prominent after the 14th day. Cerebellar symptoms, emotional disturbances and intellectual changes usually occurred during convalescence. Though most of the neurological symptoms disappeared, 30 to 40 per cent of the patients exhibited some residual findings. These were usually paralyses of eye muscles, hearing loss, tremors, cerebellar signs, Parkinsonism, impairment of mental activity, or general apathy.

Optic neuritis was noted most frequently during the third week of the disease by Hirschberg (45). Arnold (48) remarked that in no other acute infectious disease was optic neuritis so common. Optic atrophy was not uncommon (Braunstein (49), Chung (50)). Hydrocephalus has been reported by Feldman (51) and hypothalamic disturbances by Sturm (52).

Psychiatric disturbances may be prominent and usually occur during convalescence. The psychotic reactions usually contain many organic features, and mental deterioration may result from the brain involvement (Baeyer (53), Skliar (54), Munk (55), Stockert (56)).

Despite the widespread nervous system involvement the residual neurological symptoms are relatively few. Encephalitic sequelae are much less common than

are the localized and multiple neuritides (Grodski (57), Wells and Perkins (58), Lippman (59)).

The spinal fluid is under increased pressure, with a definite pleocytosis in almost all cases. Lymphocytes are present early, while in the second week large mononuclear cells appear. The protein is slightly increased, and the Weil-Felix reaction is often positive (Danielopolu (60), Heuyer (62), Kritschewsky and Autonomow (63)). Selman (64) described a case in which there occurred a sudden onset of meningeal signs in a soldier who had been given typhus vaccine 6 days previously. A marked eosinophilia was present in the spinal fluid, the cell count reaching a maximum of 670 per cubic millimeter with 78 per cent eosinophils. Slight neurological signs were present.

The pathological basis for the numerous neuropsychiatric symptoms consists of primary encephalitic process with vascular and nerve cell changes and the formation of "typhus nodules" of proliferated glial cells. These changes are found throughout the nervous system, most often associated with the smaller vessels (Wolbach, Todd and Palfrey (65), Ceelen (66), Davidowsky (67), Hirschberg (45)).

Endemic or murine typhus differs from epidemic typhus chiefly on epidemiological grounds. It is transmitted from rat to rat and from rat to man by rat fleas. The clinical features are much the same as in the epidemic form except that the symptoms are less severe and the complications are few. Maxcy (68) noted severe headaches early in the disease, followed in many cases by various combinations of dullness, apathy, nervousness, irritability and delirium. Rumreich (69) described prostration, severe headache and generalized aches and pains with, at times, irritability and insomnia. Kemp (70) recorded three cases with meningitic symptoms. Miller and Beeson (71) in review of 126 cases noted headache as the most frequent symptom and one often considered by many patients as the worst feature of this disease. In 8 cases there was slight stiffness of the neck. Frank delirium was present in 21 cases and some diminution of mental awareness was noted in an additional 28 patients. In five, the spinal fluid cell count was above 5, the highest count being 19 cells per cubic millimeter. The pathological changes in experimental animals are similar to those found in epidemic typhus (Mooser (72), Dyer, et al. (73)).

Rocky Mounted Spotted Fever. The Rocky Mountain or spotted fever group of diseases are caused by Rickettsia rickettsii and are transmitted from animal reservoir to man by various species of ticks. This group of diseases has a wide distribution and includes Rocky Mountain spotted fever of North America, Tobia fever of Columbia, Sao Paulo exanthematic typhus of Brazil, fievre boutonneuse of the Mediterranean countries, Kenya typhus in Africa and probably South Africa tick bite fever and tick typhus of India. The clinical features of Rocky Mountain spotted fever are similar to those of typhus, the chief differences being in the rash and the duration of the fever. The incubation period is most often a week or less and the onset is usually sudden with chills, a rapidly rising fever, headache, photophobia and muscle and joint pains. The diagnostic rash appears between the second and the fifth day and is first seen on

the wrists and ankles, later spreading to the arms, legs and trunk. The temperature rises rapidly, reaches its height about the second week and terminates by rapid lysis about the twenty-first day. The spleen may be enlarged and icterus and vomiting may be present in severe cases. Gangrene of the extremities may occur during the third week. The death rate ranges from 5 to 90 per cent and the prognosis is less favorable when nervous manifestations are marked.

Disturbances of the central nervous system are generally regarded as being severe, although there have not been reported the variety of symptoms that are found with typhus. Headaches, photophobia, hyperesthesias, apathy, confusion, delirium and stupor often associated with meningeal signs are the usual manifestations (Rumreich, Dyer and Badger (74), Wolbach (75), Carey and Duncan (76), Cohen (77), Crutcher (78), Hutton (79)). Marked somnolence may occur (Smith and Rheinhard (80)). Convulsions are common in children (Baker (81), Reading and Klint (82)). Nervous system complications often occur during convalescence and consist of mental confusion, deafness, impaired vision, slurring of speech, insomnia and numerous functional complaints (Rumreich (69), Parker (83) Ong and Raffetto (84)). Bennett (85) reported a case in which convalescence was complicated by episodes of seizures and coma with eventual recovery, and Palatucci and Maragoni (86) observed two cases, one with marked paresis of the legs, lasting several months, and another in which a psychotic-like episode occurred and lasted for several weeks.

The spinal fluid has been found to be under increased pressure in some cases but otherwise has been reported as negative. The fundamental pathological lesion is vascular in nature and is characterized by endothelial swelling and proliferation, sometimes going on to necrosis and vascular thrombosis. The organs most frequently involved are the skin, heart, kidney and brain. The cerebral lesions consist of a perivascular lymphocytic proliferation, perivascular and parenchymal glial nodules and micro infarcts (Lillie (87)). Aseptic meningitis and ganglion cell changes have also been noted (Hassin (88)).

Sao Paulo typhus of Brazil is both clinically and pathologically identical with Rocky Mounted spotted fever (Dias and Martins (89), Piza, et al. (90)). Similarly Topping, Heilig and Naidu (91) feel that the tick typhus in India resembles the North America disease. The fever lasts about 14 days and there is a primary sore or eschar at the site of the tick bite. There are two reports of cases with nervous system involvement (Augier and Durandy (92) Augier and Cossa (93)). These authors describe symptoms of violent headache, insomnia, muscle and joint pains, muscle rigidity and somnolence. One case showed a definite encephalitis with transient hemiplegia and extrapyramidal signs, and another case resembled tetanus with acute muscle pain, rigidity, and delirium. Paresthesias persisted for six months.

Tsutsugamushi fever (*Scrub typhus*). Tsutsugamushi fever is caused by the organism Rickettsia tsutsugamushi (R. nipponica, R. orientalis) and is transmitted to man by several species of larval mites of the genus Trombicula. This disease has been recorded from wide areas of the Orient and South Pacific. Clinically it resembles the other rickettsial diseases. The incubation period is

usually from ten to eighteen days. There may be mild prodromal symptoms, with the onset of the illness being abrupt with headache, chills and fever. The fever increases during the first week and subsides by lysis during the third week. The rash appears first on the trunk, later on the extremities. The most characteristic sign is a small necrotic ulcer at the site of the bite. There is generalized lymphadenopathy and often severe cardiovascular involvement. Convalescence is slow. The mortality rate ranges up to 15 per cent with death usually due to circulatory collapse.

Nervous symptoms are prominent. Headache, retro-orbital pain and dizziness are marked. The patients complain of generalized myalgia, backache, weakness and insomia. Williams, et al. (94) noted mental or neurological abnormalities during the course of the disease in 231, or 37 per cent, of 626 cases. Neurological symptoms included severe headache, dizziness, tinnitus, photophobia, dysphagia, paresthesias and neuritic pains. Neurological signs included hearing loss (90 cases), generally reduced or absent superficial and deep reflexes, occasional pathological reflexes (3 cases), tremors, retention and dysarthria. Paralyses and hyperesthesias tended to occur during convalescence. In one case a convulsive seizure suddenly occurred on the 29th day of the illness, two weeks after recovery from the acute stage. Following the seizure the mental condition of the patient deteriorated, and he became incontinent and unresponsive. The spinal fluid showed 168 cells, mostly lymphocytes. Recovery was gradual, marked by memory loss and transient episodes of disorientation. Machella and Forrester (96) in a series of 64 cases recorded 2 patients with generalized convulsions. Another patient had signs of marked meningismus. Scattered peripheral nerve involvement with paresthesias, transient palsies and sensory disturbances have been noted in most series of case reports (Greenfield (95), Machella and Forrester (96), Heaslip (99), Hay (100), Lipman, et al. (97)). Pathological changes in the eyes are extremely common in scrub typhus. Venous engorgement in the fundus was found in two-thirds of 451 patients (Scheie (101)). In one-third there was marked edema of the disc and retina. The retinopathy was felt to be on a vascular basis. The mental symptoms consist of euphoria, irritability, delirium, drowsiness, stupor, confusion, apathy and depression, delusions, hallucinations and late neurotic phenomena. They are most noticeable during the 6th to 10th day of illness. The delirium is often marked, producing a picture of an acute mania or a toxic psychosis (Greenfield (95), Machella and Forrester (96), Lipman, et al. (97). Lewthwaite and Savoor (98) observed such an overactivity in 35 per cent of their cases.

The spinal fluid often is under increased pressure and shows a mild pleocytosis. The pathological picture is similar to that of typhus and spotted fever. Nervous system lesions have been described by Lewthwaite (102), Kouwenaar (103), Corbett (104). The most frequent lesion consists of a perivascular proliferation of neuroglia which in some areas actually forms tiny glial nodules.

Q fever. Q fever was first described from Australia in 1937 by Derrick (105), and from the United States in 1938 by Dyer (106). It is caused by the organism Rickettsia burneti and is transmitted from the animal reservoir to man by in-

fected ticks. The clinical features are characterized by a sudden onset with anorexia, chills and fever, headache and prostration. The fever gradually falls after a week to a month and a rash is rarely seen. Pains in the back and limbs and drowsiness are present, and gastro-intestinal symptoms may be prominent, In individual cases reported by Derrick, (105) there was stiffness of the neck, "nervousness," insomnia and numbness in the hands. In one case, deafness began soon after admission and continued through a convalescence of several weeks (Morrissey and Derrick (107)). Although there are symptoms which suggest a central nervous system involvement, there is at present no pathological evidence in man to substantiate such an impression. Lillie (108) did find occasional typhus-like lesions in the brains of guinea pigs.

BARTONELLOSIS

Oroya fever or verruga peruana is a disease peculiar to Peru although recently cases have been reported in Columbia (Camargo (109), and Ecuador (Montalván and Moral (110)). This disease has been recognized for many years and has appeared in two forms: namely, as a severe febrile anemia (Oroya fever), and as a cutaneous eruption Verruga (peruana). Oroya fever has an incubation period of three weeks and is characterized by malaise and apathy, followed by a rapidly developing profound anemia and an irregular fever for about three weeks. Severe pains in the head, bones and joints are common and the spleen and lymphatic glands are enlarged. The hemoglobin is reduced to 20 to 30 per cent in two weeks and the mortality rate is high with death occurring in 2 to 3 weeks in 20 to 40 per cent of the cases. Recovery is usually followed by the eruptive or verrucous stage. Less severe or chronic cases occur in which the fever is mild, the anemia is less marked and more persistent, and a skin eruption of a nodular or miliary form appears in about 4 to 6 weeks.

Verruga peruana appears chiefly as an eruptive disease with an incubation period of 1 to 2 months and lasting 2 to 3 months. The onset is preceded by a high fever and joint pains, and the eruption is of a miliary or nodular type, with a tendency for the lesions to be hemorrhagic and sometimes ulcerative.

The causative organism was isolated in 1905 by Barton (111). It was named *Bartonella bacilliformis* in 1913 and was considered to be midway between the rickettsias and the bacilli. The organisms are found in the circulating red cells and particularly in the cells of the reticulo-endothelial system. The pathological changes in Oroya fever occur chiefly in the spleen, liver and in the vascular endothelial cells of the lymphatic system. The skin lesions present granulomatous and vascular changes with proliferated endothelial cells.

Carrion (112) first called attention to the involvement of the nervous system in this disease when he described "Verruga probably of the meninges." Since the organism is capable of affecting all parts of the nervous system, the clinical manifestations are most variable. Characteristically there have been described various forms of neurobartonellosis consisting of (1) hypertensive form, (2) meningeal form, (3) convulsive form, (4) apoplectiform type and (5) extrapyramidal form. These forms are usually mixed, giving various combinations of symptom-

atology. The so-called hypertensive form presents only symptoms and signs of increased intracranial pressure. These findings may occur either during the anemic or eruptive phase and consist chiefly of severe headaches, vomiting, vertigo, visual disturbances, mental confusion and retinal changes (Lastres (113), Monge and Mackehenie (114)). The meningeal form of the illness is usually associated with marked mental symptoms. These symptoms usually appear shortly after the appearance of the skin rash and consist of headache, stiff neck, positive Kernig's sign and delirium. The course in such cases is rapidly downhill with death in a few days (Monge and Mackehenie (114)). Convulsions in this illness was described as early as 1890 by Olaechea (115). The seizures are usually of generalized nature and appear very early in the disease and usually signify a very grave outcome. An apoplectiform type of involvement would be expected when one considers the vascular nature of the disease. In 1889 Quiroga and Mena (116) described "cerebral verruga" and cited a case of hemiplegia. Lastres (113) described a similar case in which a hemiplegia occurred three weeks after the onset of the illness and was accompanied by meningeal signs and an aphasia. The patient died two days later in profound coma. Monge and Mackehenie (114) recorded a case with hemiparesis, hemiparesthesia, cerebellar incoördination and an aphasia. Extrapyramidal system involvement is fairly common and usually occurs late in the illness accompanying the rash (Quiroga and Mena (116), Monge and Mackehenie (114), Morales (117)).

Cranial nerve disturbances occasionally accompany the above syndromes and consist of papillitis, photophobia, amaurosis, ophthalmoplegias, facial diplegias, tinnitus, deafness and vertigo. In a few cases the spinal cord may be involved, with the development of a flaccid paralysis resembling poliomyelitis but offering a much more favorable outlook (Méndez and Quintanos (118)). Symptoms of a peripheral neuritis may be present, with paresthesias, hypesthesias, motor weakness and muscle atrophy. Lastres has recently summarized the neuropsychiatric aspects of Bartonellosis (119).

The spinal fluid is often under increased pressure. The protein may be slightly elevated, but the cell count is usually normal. Neurobartonellosis may occur at any period of the disease but most often appears at the end of the hematic phase. The prognosis should always be guarded since the fatality rate in the meningo-encephalitic form is extremely high.

The pathological changes in the nervous system are widespread and consist chiefly of endothelial proliferation, occlusive thrombosis and granulomatous formation (Lastres, (113) Mackehenie and Alzamora (120)).

BACILLARY DYSENTERY

Bacillary dysentery is an acute infectious disease caused by the Bacillus dysenteriae and resulting primarily in gastro-intestinal symptoms. The disease is acute in onset with mucous and bloody diarrhea accompanied by abdominal pain, and terminating either abruptly after 4 to 6 days in death or more slowly in gradual recovery. The disease is more virulent in the tropics where it appears in epidemic form, while in the temperate regions it tends to be mild and sporadic

being most frequent in institutions or among troops during war. The outbreaks are influenced primarily by sanitation rather than by geographic distribution, and the disease is spread chiefly by contaminated food and drink. Since the isolation of the dysentery organism in 1898 by Shiga it has been recognized that the dysentery bacillus comprises a large group of microörganisms. At present the dysentery bacilli are divided into two large groups; namely, those that produce no acid in mannite sugar and no indol formation (Shiga and Kruse type), and those that do produce acids in mannito and do form indol (Flexner, Hiss, Strong type).

The dysentery bacillus is usually present in the gastro-intestinal tract where it causes a mucosal ulceration, chiefly of the large intestine. Even in the more severe lesions the organisms remain localized to the bowel rarely invading the blood stream. It is thought by some investigators that the symptoms of the disease are due almost entirely to the absorption of toxins from the intestine (Alexander and Wu (121)). Both an endotoxin and an exotoxin are produced. Olitsky and Kligler (122) obtained an exotoxin which in fractions of a cubic cm. after an incubation time of a few hours to days produced typical paralysis and severe nerve lesions in rabbits. Intravenous inoculation into rabbits produced lesions in the medulla and spinal cord similar to those seen in encephalitis.

The frequency of nervous system complications varies with the severity of the infections. Zellweger (123) in 174 cases observed such complications in 33 per cent, while von Groer (124) reported 56 per cent of his 50 cases with nervous system involvement. Alexander and Wu (121) found neurological complications in 30 per cent of 288 cases of mannite fermenting organisms and in 18 per cent of 100 cases of Shiga infestation.

The two most comprehensive studies on the clinical neurological features of dysentery have been published by Alexander and Wu (121) in 1934 and by Zellweger (123) in 1943. Alexander and Wu reviewed 594 unselected cases occurring in China during a 12 year period in regard to symptoms of nervous disorders. Among 288 cases of mannite fermenting dysentery they found 5 cases of neuritis, 9 cases with single symptoms such as drowsiness, restlessness or convulsions, and 73 cases with general symptoms such as mental dullness, apathy, restlessness, irritability, headaches, dizziness, tinnitus, lethargy, stupor and irregular reflexes. In 100 cases of Shiga bacillus dysentery, there were 18 children under the age of 5 years with nervous system involvement. Of these, 5 had neurological symptoms, chiefly convulsions, with 3 deaths, and the remaining revealed severe general symptoms such as somnolence, lethargy, vertigo and restlessnesss. Zellweger divided the neurological complications into two groups: namely, early complications involving the central nervous system and affecting chiefly children and the late manifestations involving the peripheral nervous system and occurring usually in adults. The most striking central nervous system symptoms consisted of meningismus, paresis and convulsions. These were usually transient and disappeared early in the illness. The late complications involving the peripheral nervous system produced neuritis, radiculitis and even Landry's type of paralysis. Two cases of polyneuritis were

recorded and bulbar symptoms of dysphagia, nasal speech and a left facial palsy, with subsequent recovery were seen in a 6 year old boy. The onset of the neural manifestations usually took place after the dysentery had been present for some time, but in 20 of 32 of Zellweger's cases the neurological and abdominal symptoms appeared simultaneously while in 7 cases nervous symptoms of headache, vertigo and irritability preceded the abdominal symptoms by 2 to 4 days.

Deshmukh (125) reported a case of dysentery meningo-encephalitis occurring in a 4 year old child in which the meningeal symptoms were striking, while Hofstede (126) described a case in which there suddenly developed a typical Parkinsonian syndrome 5 days following the onset of a Shiga dysentery in a Chinese boy. The condition continued for one week and gradually improved. Peripheral nerve involvement usually occurs in adults during the second to fourth week of the illness and may take the form of a mononeuritis or a polyneuritis (Müller-Deham (127), Alexander and Wu (121), Zellweger (123)). The mononeuritis may implicate any of the nerves but most often involves the sciatic. The polyneuritis results in paresthesias, hypesthesias, anesthesias, lower motor neuron weakness and rapid atrophy of the involved limbs. Trophic changes are frequent in such cases. Singer (128) reported a case of a 34 year old male who two weeks following an infection with the Shiga bacillus developed paresthesias in the finger tips and toes. Two weeks later he developed hypesthesia of the left arm and subsequently noted weakness of the left arm and leg. The weakness began to clear up in two weeks. Three other cases had peripheral sensory disturbance with weakness and atrophy. In another report Singer recorded 30 cases with a long lasting peripheral neuritis following dysentery.

Spinal fluid examination may be normal or may show a slight pleocytosis and a mild elevation of protein. Zellweger (123) observed pleocytosis in 7 out of 32 cases, the highest count being 26 cells.

In general, bacillary dysentery is a self-limiting disease, running its course in ten days to two weeks, but chronic cases may occur with episodes of diarrhea continuing for years. The prognosis in uncomplicated cases varies with the severity of the infection. Kamar (129) reported a mortality rate of 6.2 per cent in 772 cases. In the presence of neurological complications, however, the mortality rate increases rapidly and a death rate of 66.4 per cent in 143 cases has been reported (Kamar (129)). Generally the milder complications such as meningeal symptoms, headaches, vertigo and restlessness disappear shortly after the onset of the gastro-intestinal symptoms. In scattered cases the neurological complications persist for many years as permanent sequellae of the disease. Burnet (130), Comby (131), Zellweger (123) reported isolated motor involvement persisting years after recovery. In Comby's cases, one patient showed a hemiparesis one year later, while another developed an impaired speech. Mensel (132) reported 2 cases in which an incoördination of all limbs persisted 12 years after the acute infection. One patient showed, in addition, some tremor, atrophy and paresis of the arms, while the second complained of hypesthesia of the extremities.

Lenhartz (133) described a case of an 8 year old boy who shortly after the

onset of dysentery developed delirium followed by apathy and unresponsiveness. As the patient began to respond, aphasia and ataxia were noted. After 2½ years the boy still was ataxic and showed marked mental deterioration.

Pathological changes in the brain show sporadic ischemic areas in the cortex with altered nerve cells and proliferating glial elements (Alexander and Wu (121)). Ring and ball hemorrhages may occur (Buttenwieser (134)).

CHOLERA

Cholera is an infectious disease caused by the bacterium Vibrio cholerae. This disease primarily affects the intestinal tract resulting in severe purging diarrhea, vomiting, muscle cramps, anuria and collapse. It is spread from man to man by fecal contamination of food and water. Cholera has been endemic in India for centuries, and the delta of the Ganges constitutes at the present time one of the principle foci for the spread of the disease, though other endemic centers exist in China and other Far Eastern countries. From these endemic centers spread the various epidemics and pandemics that have swept the world.

The clinical course of cholera usually begins abruptly with the stage of evacuation characterized by severe diarrhea, rice water stools, vomiting, prostration, agonizing muscle cramps and a rapid dehydration. This stage is but a few hours in duration and is followed by the stage of collapse or algid stage in which there is almost complete cessation of the circulation. Death may occur from respiratory failure or uremia, or the patient may go on to the stage of reaction, with a return of circulation and recovery in about a week. The most common complication is persistent anuria and uremia. The death rate is about 50 per cent in the untreated cases and about 20 per cent in the cases treated with intravenous fluids. The initial pathological change is a desquamation of the epithelium of the intestinal tract which is caused by an endotoxin liberated from the cholera organism. Subsequent changes are associated with the severe dehydration, circulatory collapse and uremia.

Cerebral complications in cholera are almost never mentioned in the usual descriptions of this illness in spite of their recognition in a number of reports in the literature. Often the clinical symptoms referable to the central nervous system are so mild and non-specific as to be entirely overlooked (Bourgogne (135)). Mild prodromal symptoms of disturbed sleep and difficulty in thinking may be followed by specific complaints of vertigo, headaches, restlessness, convulsions, apathy progressing to stupor or severe delirium. Probably the most frequent complications are the convulsions and the motor involvements, both occurring during the acute illness or after recovery. Gavino (136) reported convulsions as a frequent finding during the acute phase, particularly in children. Weber and Ranke (137) described a case in which generalized seizures appeared on the second day of the illness. These were followed by a deepening somnolence accompanied by delirium, with a fatal termination on the seventh day. Delasiauve (138) noted a case in which severe generalized seizures developed 1 month after apparent recovery from cholera. The patient ultimately recovered. Burq (139) divided convulsions in cholera into symptomatic and

essential types. The former, he believed, was due to actual central nervous system involvement, the latter to some myogenic factor. Motor involvement in the form of weakness or paralysis, although less common than the convulsions, have been described by Jaubert (140) and Gubler (141). In both cases the onset of the paralysis was very slow, the patient appearing weak and listless for days. The paralysis soon involved the entire one-half of the body and continued until the patient died (Gubler) or left the hospital (Jaubert). In other cases, scattered and often extensive areas of hypesthesias have been observed (Jaubert).

Even more common than the neurological complications in cholera are the mental disturbances which may be most variable in nature and most irregular in the time of onset (Obregia and Pitulesco (142), Kraepelin (143)). Curiously enough, these psychic disturbances almost never occur during the height of the illness but more commonly appear a few days after recovery. Delirium is most common (Kraepelin (143), Mesnet (144), Ball (145), Krempin (146)). There is great motor unrest with rapid mood changes from exaltation to depression. The patients become disoriented and often have visual and auditory hallucinations. The delirium continues for a few days to a week and invariably clears up abruptly. A few patients developed a severe and prolonged melancholia following recovery from the acute illness (Delasiauve (138), Atkinson (147)). Delasiauve (138) described a case in which an expansive delusional picture not unlike that of a general paretic developed one month after recovery from cholera. Recovery from the psychosis was slow but complete. In most of the psychic complications of cholera the ultimate outlook is favorable and many of the patients have a complete amnesia for the attack (Kraepelin (143), Lewtschatkin (148), Ball (145), Griedenberg (149), Wassilieff (150)). In about 15 per cent of these cases, neurological disturbances such as epileptiform seizures, speech disturbances, tremors, etc. accompany the psychic picture (Kraepelin (143)).

A number of studies have been published describing pathological changes in the brain in cholera. Diffuse destruction of cortical nerve cells was the most common finding (Iwanowsky (151), Popoff (152), Tschistowitch (153), Pines (154)).

PLAGUE

Plague is an acute infectious, highly fatal disease of man and rodents caused by the bacterium Pasteurella pestis. Bubonic plague, the classical form of the disease, is characterized by inflammatory enlargements of the lymph glands (buboes) and is transmitted from infected rats or other rodents to man through the medium of fleas. Pneumonic plague is a rapidly fatal primary pneumonia transmitted directly from man to man through droplet infection. Other types of plague have been described such as septicemic, carbuncular and cerebral forms (Simpson (155), Choksy (156)).

This disease is one of great antiquity and a number of pandemics have spread into Europe from Asia and the Middle East. The last great pandemic was world-wide, originating in China in 1894 and reaching the United States in 1900.

India and China still constitute major endemic centers. Since plague is primarily a disease of rodents, there exist a number of localities in the world which constitute important endemic foci of sylvatic plague with the disease firmly intrenched in the native rodent population. In the United States, sylvatic plague is most common in ground squirrels and is at present gradually extending eastward from the western states, North Dakota being the present limit of spread.

The incubation period of bubonic plague is usually from 3 to 4 days. The onset is abrupt, with chills and a rapidly rising fever. Severe headache and backache are present and symptoms indicative of cerebral involvement are striking. Buboes in the groin and axillary region develop within the first two days. Prostration, a rapid feeble pulse and petechial hemorrhages in the skin are present in severe infections. Death usually occurs before the fifth day, and if the patient survives the buboes may suppurate and the illness may last for several weeks. The mortality rate is from 50 to 90 per cent in severe cases. In pneumonic plague the chief symptoms are chills and fever, cough, dyspnea and anxiety. This form of the disease is almost 100 per cent fatal and death occurs a day or two after the onset. In septicemic plague, the organisms enter the body through the mucous membranes, and the course is that of a rapidly fatal septicemia, death occurring in a day or two.

The principle pathological findings in plague are the marked inflammatory and hemorrhagic changes in the lymphatic glands, and the widespread destruction of the endothelial lining of blood vessels from the toxin produced by the bacillus, resulting in generalized congestion and extravasations of blood throughout the tissues. At autopsy the bacilli can be obtained from many organs, including the spinal fluid and brain (França (157)). Pathological studies of the brain have shown a meningitis, venous thromboses, hemorrhages and acute and chronic nerve cell changes. Plague bacilli were found in the thrombosed vessels, in the white matter and in the cortical neurons and adjacent tissue (França (157), Nepveu (158), Lien-Teh (159), Crowell (160)).

The cerebral involvement is extremely common in plague and frequently constitutes the predominating symptomatology. Such symptoms were recognized in very early epidemics and were described by Procopius (161) as early as 542 A.D. as follows, "Some were stricken with heavy lethargy, others with raving madness, but each and all suffered what was in keeping with these results. Those who were weighed down with lethargy always seemed to be asleep, forgetful of their usual avocations. If there was anyone present to look after them they would take food at times, those who had no one to attend to them perished for want of food. But the delirious, unable to sleep and thinking everyone ready to murder them were struck with terror and shrieking horribly tried to flee away."

Premonitory symptoms seldom occur and where present usually consist of anorexia, malaise, frontal headache, nausea and vomiting, weakness, vertigo and pains in the limbs (Simpson (155)). In most cases the onset is abrupt and is accompanied by severe headache, vertigo and mental dullness. The headaches and vertigo increase in severity and persist throughout the course of the disease (Botreau-Roussel (162)). The eyes become congested, the face drawn and

anxious. As the disease progresses the severe toxemia affects the intellect and the mental dullness increases, going on to confusion and delirium. In some cases consciousness is retained to the end, but even in these there appears considerable lethargy and mental retardation. Usually, however, the final stages are marked by periods of coma and a deep stupor terminating in death (Strong (163)). Delirium, when present, may be mild or severe and may alternate with periods of lucidity or with periods of lethargy and stupor. In the milder forms, the patient is restless, irritable, muttering and mildly confused. Hallucinations may be present. More frequently the delirium is very violent, with extreme psychomotor excitation and terrifying and bizarre hallucinations. Sleep is obtained in snatches and there is a great desire to wander from place to place. Such patients may be both homicidal and suicidal (Simpson (155), Strong (163), Rau (164), Augagneur (165)).

In septicemic plague, because of the overwhelming blood stream infection, the cerebral symptoms develop with great rapidity. The onset of the illness is extremely abrupt with rigors, intense frontal headaches, vomiting and extremely high fever. Prostration may be so great that the patient passes directly into a stage of lethargy, stupor or coma. In many cases the stupor is preceded by a short period of extreme excitation and restlessness. In an occasional case of septicemic plague and in many cases of pneumonic plague the patients do not show signs of grave infection. Such patients remain clear until sudden circulatory collapse and death (Choksy (156)). Rau (164) in an outbreak of pneumonic plague in Brazil reported many patients who showed a period of euphoria lasting minutes or hours shortly before death.

Most of the general symptoms no doubt are due to the extreme toxemia occurring in this disease. Since the plague bacillus actually localizes within the meninges and brain substance one would expect focal symptoms to accompany the more general symptoms already described. The most characteristic of these focal phenomena are the ataxic gait and an incoördination of speech (Lien-Teh (159), Simpson (155)). The gait often resembles a drunken individual and there may be incoördination of the hands. There is no accompanying paralysis except for the weakness due to exhaustion. The speech frequently is peculiarly hesitating and stuttering, thick and indistinct from loss of power to coördinate muscles of articulation. Aside from these ataxic symptoms the patients may develop tremors, twitchings, particularly of the muscles of the face, neck and extremities and even convulsive seizures (Kitasato (166), Haffkine (167), Renaud (168)). The pupils may be enlarged, the reflexes may be unequal and hearing may be impaired (Lien-Teh (159)). Finally, de Villafane, Lastra and Rocleiro (169) described four cases of meningeal plague in which neck rigidity, Kernig's sign and increased cerebrospinal fluid pressure comprised the outstanding clinical features of the illness.

MELIOIDOSIS

Melioidosis is a tropical infection of rats which in man produces a disease resembling glanders. It was first recognized by Whitmore and Krishnaswamy

(170) in 1912 and by 1933, 95 cases had been described from the Malay States, Netherland Indies, Ceylon, Burma, China and Indo-China. The disease is probably spread to man through the ingestion of foodstuffs contaminated by excreta of wild infected rats. Clinically there is no characteristic symptomatology. The acute septicemic form resembles a plague or cholera with fulminating onset, vomiting, diarrhea, extreme prostration, delirium, stupor and death within a few hours (Gambier (171), Toullec and Huard (172)). The temperature usually is extremely elevated and circulatory collapse often ensues before death. Some cases are slower with a course lasting from days to weeks (Roton (173), Mesnard et al. (174) Vielle et al. (175), Letonturier et al. (176)). In these cases the temperature often remains elevated and the patient complains of severe headaches, myalgia, nuchal pain and occasionally of meningeal irritation. Roton (173) observed a fatal case in which sphincter disturbances occurred. In Vielle, Morin and Messeas' case a 33 year old male developed a sudden onset of fever associated with myalgia, headache and erythema of the face. Five days later he became delirious and soon passed into stupor associated with meningeal symptoms and muscle tremors. Death ensued in a few hours. The mortality rate in this disease is very high. Pathologically, the characteristic lesion is a small yellowish caseous nodule. The lesions have been reported in all organs except the brain, though the clinical picture of the central nervous system symptoms suggests the probability of cerebral involvement.

LEPROSY

Leprosy is a well known infectious disease which has been recognized in man since great antiquity. It is estimated that there are some three million cases in the world, by far the greater number being in the tropical regions of Africa and Asia. According to McCoy (177) there are 400 to 500 active cases in the United States.

The leprosy bacillus Mycobacterium leprae has been accepted as the causative organism and is present in large numbers in the characteristic lesions throughout the body as well as within the peripheral and even the central nervous system. There is some question about the occurrence of the leprosy bacillus within the circulating blood, but it is believed by Strong (178) that it is through the blood that the bacilli are spread from organ to organ. Cases of the disease probably owe their origin to contact with an active case over a long period of time but the exact method of spread or portal of entry of the infective organism is not known.

There are two well recognized types of the disease. The nodular or skin variety is characterized by a granulomatous proliferation within the skin and subcutaneous tissues to form the so-called leproma. These consist of a mass of leprosy or foam cells often filled with leprosy bacilli and intermixed with various types of connective tissue. The second type is known as the maculoanesthetic or neural type and is characterized by the development of cellular proliferation about the nerves, with thickening of the nerves, areas of anesthesia, muscular palsies and atrophies, and trophic changes with eventual contractures and mutilations.

Clinically the disease has an incubation period of from one to ten years, being shorter in children. The early manifestations are vague and consist of malaise, easy fatigability and the appearance of pigmentary changes in the skin or areas of anesthesias, sometimes associated with neuralgic pains. The course naturally is slow and insidious often becoming arrested for many years. The skin becomes thickened and more anesthetic and nodules develop, particularly in the skin about the face and in the mucous membranes of the nose, mouth and larynx. The nodules tend to ulcerate with the formation of various scars and deformities. The neural lesions lead to palsies, muscular atrophies, and tropic changes within the extremities occasionally resulting in the absorption of the terminal phalanges and chronic ulceration.

Occasionally during the course of the illness certain special symptoms may occur which suggest a more specific involvement of the nervous system. Many patients, especially at the beginning of the illness, show a tendency toward somnolence and complain of severe headaches. Often this somnolence is associated with frequent nightmares of a terrorizing nature, visual hallucinations and an agonizing sensation of stuffiness. Motor and sensory manifestations are chiefly referable to involvement of the peripheral nervous system. The motor paralyses are almost always of a flaccid type. Looft (179) did report one case in which the patient died in convulsions.

Mental symptoms have been reported in many cases of leprosy (Bodros (180), Jakob and Meggendorfer (181), de Beurmann et al. (182), Muir (183), Jones and Pearson (184), Swerbejew (185)). All forms of psychoses have been observed. Some have been assumed to be due to the cachexia, some have been suspected to be accidental, while a small group have been assumed to be precipitated directly by leprosy and probably due to the organic brain damage resulting in this disease. A large group of the mental disturbances in leprosy no doubt result from the patients' social rejection and isolation and the physical suffering which they undoubtedly undergo. Varying emotional disturbances occur from simple states of anxiety, agitation and insomnia to complete breakdowns manifested in a picture of depression or even paranoid states. Cozanavette (186) found 19.5 per cent of 427 patients at the U. S. National Leprosarium to be suffering from mental disorders. Some patients show a toxic psychosis associated with confusion, delirium, hallucinations and even dementia (Swerbejew (185), Bodros (180), Jones and Pearson (184)), and it is these cases that bring up the question as to whether the leprosy bacillus or a toxin does produce the organic psychosis. Jones and Pearson (184) reported a case of an intellectually brilliant 21 year old girl who developed a confusional insanity a number of years after developing leprosy. She deteriorated rapidly, became disoriented in all spheres and showed a marked impairment of general intelligence as well as memory and emotions. Jakob and Meggendorfer (181) reported a somewhat similar case in a 25 year old male who had had leprosy since the age of 10 years. The patient died and autopsy studies revealed generalized organic brain damage. Occasionally this form of psychosis is associated with a polyneuritis, producing a syndrome fairly characteristic of that described by Korsakoff (de Beurmann, Roubinovitch and Gourgeret (182)).

Naturally, the appearance of such an organic psychosis in leprosy, as well as the appearance of the bacilli in the circulation, make one consider the possibility of an actual leprosy encephalitis with definite changes in the central nervous system. While many investigators who have studied the brain in leprosy believe that no definite changes occur (Thoma (187), Neisser (188), Leloir (189), Gerlach (190), Rikli (191)), others have found definite cerebral alterations (Vilde (193), Dwijkoff (192), Stahlberg (194), Jakob and Meggendorfer (181)). In general the involvement was diffuse, with definite nerve cell destruction, vascular congestion and various glial changes. Inflammatory elements were not marked.

MALARIA

The importance and prevalence of malaria need hardly be emphasized. It is world-wide in distribution, though more frequent and more severe in the tropical and sub-tropical countries with cases numbering in the hundreds of millions. It is caused by various species of protozoa parasitising the red blood cells and is transmitted to man by the bites of infected anopheles mosquitoes, the definitive host. It is characterized clinically by periodic attacks of fever associated with anemia and splenomegaly. There are three well recognized types of this disease. The most common is the benign tertian type caused by Plasmodium vivax. This form is the most widespread and is the most frequent form seen throughout the temperate zones. Quartan malaria is relatively infrequent and is caused by Plasmodium malariae. Aestivo-autumnal or malignant tertian malaria is caused by Plasmodium falciparum and is encountered chiefly in the badly infected districts in the warmer parts of the world. It is the prevailing form in India, Southern China and Central Africa, and is by far the most dangerous form because of its tendency to produce pernicious and malignant manifestations, especially in regards to the central nervous system. The term cerebral malaria is generally used to designate an infection of the malignant tertian type in which symptoms of a central nervous system involvement are prominent. In a recent series of 6,059 cases of malaria there were 140 cases of cerebral malaria or 2.3 per cent (Fitz-Hugh et al. (195)). Benign tertian or vivax malaria may also give rise to cerebral symptoms, though they are infrequent and usually not severe. In a series of 48 cases of cerebral malaria at the John Gaston Hospital, three were found to be caused by P. vivax. A wide variety of cerebral symptoms have been described in other reports on cases of vivax malaria (Most and Hayman (196), Hyman (197), McGinn and Carmody (198), Harvey (199)). The cerebral symptoms in this type of malaria have been assumed to be due to a severe toxemia rather than to definite cerebral changes by the invading organisms as seen in cases of P. falciparum infections.

The clinical picture in cerebral malaria is most variable since almost any part of the brain may be involved. This has led to the description of numerous types of cerebral malaria such as "meningeal type," "encephalitic type," "cerebellar type," "myelitic type," "hemiplegic type," etc. The onset of this syndrome varies within wide limits. Many of the patients are admitted in coma, convulsions, delirium or various stages of lethargy. In most cases, however, a careful history will reveal some premonitory symptoms during the preceding days

consisting of headache, nausea, vomiting, backache, nuchal pain, photophobia and vertigo. Generally the most common early complaints are intense headache, somnolence and disorientation (Hughes and Bomford (200), Fitz-Hugh et al. (195)). In rare cases the headaches may comprise the only indication of cerebral involvement and may disappear after treatment (Stedman (201)). Generally the headaches are followed after a few days by the dramatic appearance of more severe symptoms such as coma, delirium or convulsions.

The coma is so common that cerebral malaria is often referred to as malarial coma. It may be acute in onset following a few hours or days of intense headache and disorientation or it may be very insidious in occurrence, being preceded by a long period of delirium, fever and increasing lethargy (Sanford et al. (202), Brennan (203), Whitehill (204), Kneedler (205), Sneddon (206), Don et al. (207)). The extent and depth of the coma varies considerably and it is usually accompanied by a high fever. Even when the coma appears without pyrexia, the temperature usually soon rises to alarming heights. In some patients the coma is transient especially under treatment but when recurring it usually carries a poor prognosis (Sneddon (206), Kneedler (205)). The appearance of sudden coma in a patient with or without prodromal symptoms and sometimes without fever may suggest syndromes other than malaria and treatment may be unfortunately delayed.

Delirium, although an accompaniment of any type of fever, in the presence of falciparum malaria is more likely to be a sign of cerebral involvement (Kneedler (205), Masson (208), Simpson and Sagebiel (209), Lecler (210)). In the milder cases, the delirium may appear only during paroxysms of fever. In the more severe cases, the delirium is more intense resulting in complete disorientation, incoherence, motor agitation often progressing to a full blown acute mania with screaming, laughing, crying and terrifying hallucinations and delusions. These severe attacks of delirium may be followed by coma or convulsions, both of which may disappear with the fall of the temperature or may terminate fatally, especially if no treatment is given. Convulsions are a frequent manifestation of cerebral malaria, especially in children though they are not as common as is coma (Eckstein (211), Whitehill (204), Marinesco (212), Simpson and Sagebiel (209), Kneedler (205)). During the vivax infection the convulsions are considered as being mainly the result of the high fever (Most and Hayman (196)), but in falciparum infections they are thought to be due to actual brain involvement. The convulsions may be one of the initial symptoms and are accompanied by or followed by a high fever. Patients may sometimes be admitted to the hospital with a diagnosis of epilepsy (McGinn and Carmody (198)). The convulsions are usually generalized though they may be Jacksonian in type and they may occur but once or in repeated attacks. Severe seizures are as a rule accompanied by coma though some patients may develop only generalized tremors and myoclonic movements without loss of consciousness (Marinesco (212), Arbuse (213)).

Aside from the above more common symptoms, cerebral malaria may present numerous and varied localizing symptoms consisting of hemiplegias, monoplegias, paraplegias, aphasias, ataxias and extrapyramidal system signs. Symptoms of

cerebellar involvement are especially prominent (Dairla (214), Still and Lal (215), Mendez and Huaman (216), de Vries (217), Simpson and Sagebiel (209)). The motor involvement may be both of a flaccid or spastic type (Hurd (218), Suckling (219), Stockwell (220), Gupta and Laha (221), Skobsky (222), Kneedler (205)). Skobsky (222) reported a classical case of ascending flaccid paralysis of Landry with recovery after antimalarial treatment. The extrapyramidal symptoms usually appear late in the illness during convalescence (Kneedler (205), Fornaca (223), de Brun (224)). Bulbar symptoms have been observed and are quite variable. Cranial nerve involvement may be present in both falciparum and vivax malaria (Talbot (225), Arbuse (213), Harvey (199)). Optic neuritis may be present (Robertson (226)) and aphasia may occur (Rao (227), Dee (228), Gillot (229), Arbuse (213)). In some cases the cerebral involvement is so scattered that the patient presents a picture resembling multiple sclerosis (Boinet and Salebert (230), Spiller (231), Triantaphyllides (232)).

In view of the varied cerebral involvement almost any type of neurological findings may be expected. These may be transient and subject to rapid change. Meningeal signs and symptoms frequently occur and the clinical picture may simulate epidemic meningitis. In such cases the spinal fluid is found to be clear under normal or increased pressure and with only slight pleocytosis (Narayan (233), Wright (234), Simpson and Sagebiel (209), Eckstein (211), Whitchill (204), Hyman (197)). Multiple neuritis is a rare occurrence in malignant tertian malaria but has been reported (Kneedler (205), Eckstein (211), Joelsae (235)). Harvey (199) described a peculiar type of neuritis in 16 cases of vivax malaria which consisted of the association of hyperalgesia, hyperhidrosis and increased muscle tone with actual contractions occurring in bilaterally symmetrical areas, usually in the forearm and hand.

Psychiatric manifestations in malaria are of very frequent occurrence (Kraepelin (236), Pasmanik (237), Parot and Gutmann (238), Forrester (239), Arbuse (213), Masson (208), Berlin (240), Wright (234), Eckstein (211)). The delirium and coma accompanying the cerebral involvement have already been discussed. Data on malarial psychoses is difficult to clarify due to the fact that this disease infects so great a number of people each with his own individual personality makeup and subject to a different emotional pattern. The varied mental pictures can only be proven to be due to malaria by the response to drug therapy. Pasmanik (237) observed mental involvement in 106 of 5412 cases of malaria. Gehrenstein (241) found depression as the most frequent feature although, generally, the malarial psychoses has been described as confusional in type (Parot and Gutmann (238), Arbuse (213)). The mental picture, regardless of its form, is usually followed by an amnesia, often of a retrograde type. Mental symptoms may occasionally result from atebrine therapy, but these usually clear up when the drug is discontinued (Gordon et al. (242), Bispham (243)).

In many cases of malaria, particularly in the benign tertian form in which the illness becomes chronic, definite mental symptoms of a neurasthenic nature develop. There appear depressive trends, irritability, nervousness and numerous somatic complaints (Pope (244), Atkinson (245), Musgrave (246)). Tumulty

and his associates (247) found fatigability to be the chief manifestation in 50 cases of recurrent malaria. It was expressed by mental apathy and was measurable objectively by means of the Rorschach tests. The patients' chief complaints were weakness, tension, excessive sweating, headache, dyspnea, anorexia, palpitation, "blackouts" and insomnia. Zeligs (248), on the other hand, felt that "post malarial asthenia was not associated with recurrent malaria." He did note severe headache between attacks to be a most disturbing symptom, often giving rise to secondary neurotic-like phenomena.

The course and prognosis in cerebral malaria varies with the severity of symptoms and the promptness with which treatment is instituted. In Fitz-Hugh et al. (195) series of 140 cases the mortality was 25 per cent. Patients with both coma and convulsions had an 80 per cent mortality rate. Generally, the mortality rate in malarial coma is 40 per cent if treated (Kneedler (205)), while if untreated very few recover. Long continued cerebral symptoms even under treatment carry a guarded prognosis, although cases have recovered who have been in coma more than a week.

The pathological lesions in cerebral malaria have been described in numerous reports. Generally they consist of vascular thrombi with hemorrhages, focal perivascular areas of necrosis and gliosis, and diffuse nerve cell changes.

AFRICAN TRYPANOSOMIASIS

African trypanosomiasis, or sleeping sickness, is caused by the hemoflagellate Trypanosoma gambiense, which is transmitted from man to man by various species of tsetse flies. The infection is characterized by an irregular fever, adenitis and a meningo-encephalitis with symptoms of physical and mental lethargy. It is confined almost entirely to Equatorial Africa and is severe in some districts, being about 100 per cent fatal without treatment. Wild and domestic animals may be a reservoir of the disease.

Clinically the disease progresses from an early acute or incubation stage lasting from a few months to several years to a terminal cerebral or "sleeping sickness" stage. The incubation period is from two to three weeks though some individuals may harbor the parasite for several years before showing symptoms. The first sign of the disease is usually a fever followed by glandular enlargement, edematous swelling about the eyes and joints, and occasionally a rash. Enlargement of the post-cervical glands is frequently found and is of diagnostic importance. Headaches, neuralgic pains and deep hyperesthesias are usually present. There may be insomnia and difficulty in mental concentration in this stage of the illness and delirium is occasionally seen during the fever (Van Zyl and Gear (249)). These symptoms may be mild and disappear either spontaneously or with treatment, or they may gradually progress to the cerebral stage.

The cerebral stage is characterized by the advent of various neurologic and psychiatric manifestations. Tremors, weakness, spasticity and personality disturbances become evident and as the disease progresses the typical deterioration, emaciation and somnolence gradually increase until death intervenes. This stage usually begins early in the second year and lasts from a few weeks to several

months or years. It is highly fatal and death occurs from terminal meningitis, pneumonia or other secondary infections.

The pathological changes consist chiefly of a chronic inflammation of the lymphatic system and a diffuse meningo-encephalitis with a somewhat greater degree of involvement of the white matter than of the cortex (Bertrand, Bablet and Sicé (250), de Savitsch and Freeman (251), Mott (252)).

Clinical evidence of nervous system involvement may be slight or even absent for a considerable time, even after the spinal fluid changes indicate definite cerebral invasion (Sicé and Leger (253), Sicé (254), Bertrand (255), Duren and van den Branden (256)). The first indications of encephalic involvement are usually subjective in nature and consist in slight changes in the mental attitude of the patient, manifesting itself in irritability, apathy, fatiguability and various somatic complaints (Low and Castellani (257)). As the disease advances more definite encephalitic signs and symptoms develop. The superficial reflexes are generally normal. The deep reflexes tend to be exaggerated at first but later become diminished or absent. Pathological reflexes, clonus and reflex inequalities may be observed. Abnormal muscular movements are usually prominent and consist of a fine tremor of the tongue accompanied by tremors of the hands and occasionally of the whole body. Sicé and Moreau (258) noted a case in which the only apparent cerebral symptoms consisted of tremors of the tongue and fingers and slight reflex alterations. Marked changes in the spinal fluid with the presence of trypanosomes confirmed the diagnosis.

Convulsive seizures have been observed by many investigators (Pinard et al. (262), Van Zyl and Gear (249), Moustardier (263), de Savitsch and Freeman (251)). Moustardier (263) described a case in which the first symptoms of infection were epileptiform convulsions. As the disease progresses, muscular weakness and atrophy develop so that the patient ultimately becomes totally helpless and bed-ridden. Paralyses of various muscle groups may occur. Vix (259) observed a hemiplegia in 6 out of 70 cases. Fain (260) reported hemiplegia associated with aphasia.

Extrapyramidal system involvement is not uncommonly seen in this illness. Rigidity is extremely frequent in advanced cases and Sicé, et al. (261) have observed an increasing number of cases of parkinsonism following sleeping sickness. Choreiform movements are less frequent but have been reported.

Gait disturbances form one of the distinctive symptom patterns. A slight ataxia may be noted relatively early in the development of nervous symptomatology. The patient will occasionally stumble and notice difficulty in climbing stairs before his gait becomes typically shuffling. A positive Rhomberg sign may be present and various cerebellar disturbances are common and striking, especially as the encephalic involvement becomes more obvious.

Disturbances in sensation are not marked in trypanosomiasis except for the prominent deep hyperesthesia (Kerandel's sign). This is present during the acute stage and usually disappears as the disease advances, the patient becoming insensitive to all stimuli. Areas of superficial hyperesthesia and hypesthesia have occasionally been described.

Cranial nerve findings include optic atrophy, nystagmus, facial paresis, deafness and weakness of the tongue. Bertrand (264) felt that the optic atrophy frequently described was often due to the treatment with arsenicals; however, optic atrophy does occur in individuals without treatment. Slurring of the speech is frequently observed. A case of congenital hydrocephalus with parasites in the spinal fluid has been reported (Darré et al. (265)).

Psychiatric manifestations are almost universally present and occur throughout the course of the infection. Long before the typical lethargy and somnolence appear there are many indications of cerebral infection. Listlessness, apathy and sometimes irritability appear. The patient may find it difficult to think and to comprehend and memory becomes impaired. Impatience may also occur. The slight personality changes frequently progress to more serious disturbances with delusions and hallucinations. Acute maniacal episodes are fairly common. Cataleptic symptoms were noted by Christy (266) and a toxic psychosis with marked paranoid features was described by Kirschbaum (267). The psychiatric picture occasionally resembles that seen in general paresis with expansive delusions and deterioration. As the infection continues, the cardinal symptoms of apathy and lethargy become more obviously superimposed on the clinical picture. The features become dull and the patient gradually becomes more and more retarded. The sleeping is rather an extreme apathy than true somnolence since the patients can easily be roused. Mental deterioration is gradual with general loss of interest in the environment, mental confusion, forgetfulness and regression. The patient forgets to swallow his food, saliva drools from his mouth, becomes emaciated and drowsiness gradually increases to a state of coma and death.

The spinal fluid changes are characteristic and may be present early in the course of the disease. Barlovatz (268) found the spinal fluid to be more useful than the blood for diagnosis. He noted a meningeal reaction early and for this reason suggested that there actually was but one stage to this infection, the cerebral involvement being present from the onset.

Barlovatz (268) observed spinal fluid changes in 85 to 90 per cent of infections. In another study, Bertrand (255) reported spinal fluid changes in one-third of those patients in whom trypanosomes were found in the blood or lymph glands and in whom there were no clinical symptoms. The first change in the spinal fluid usually occurs several months to a year after the onset of the illness and consists in an increase in the number of cells from 10 to several thousand per c.c. The number of cells is somewhat proportional to the intensity of the cerebral infection. In acute cases the cells are mostly lymphocytes while in more chronic cases there are, in addition, plasma cells, endothelial cells and "morula cells." The albumin gradually rises to levels of 1 gram or higher and roughly parallels the cellular reaction. There is a tendency for the protein to return to normal values in chronic cases and cases close to death. The fluid is clear in spite of the high cell counts (Sicé (269)). The colloidal benzoin test is usually positive.

SOUTH AMERICAN TRYPANOSOMIASIS

South American trypanosomiasis or Chagas's disease is caused by the flagellate Trypanosomia cruzi. It was first described in 1909 by Chagas who found that the disease was transmitted from animal reservoir to man through the bite of a species of Reduviidae bug. In man the parasite invades the endothelial and other cells causing cellular infiltration, degeneration and eventual fibrosis of the affected tissues. In the blood stream, the organisms are in the form of trypanosomes while in the tissues they assume a leishmania-like form, with a small round body containing a nucleus and a kinetoplast. Acute and chronic forms of the disease are described. In the acute stage the parasites are in the circulating blood and produce fever, edema and adenitis. In the chronic stage, the symptoms are produced by the parasites as they become localized in various tissues of the body, especially the heart and brain. The disease is most common in infants and young children. It is among this age group that the acute form results, with a high mortality rate. Adults infected experimentally have suffered only mild symptoms, and in many the disease has been discovered only by routine examination of the blood. Cases of Chagas's disease are numbered in the hundreds and are widely scattered over South and Central American, being most common in Brazil and Argentina.

Following an incubation period of from 1 to 2 weeks the acute attack usually begins with a high fever of intermittent or continuous type. A week or two later there occur various edematous swellings, particularly about the face and eyes. The ocular edema is often unilateral and accompanied by conjunctivitis (Romano's sign). The spleen, liver, thyroid and lymphatic glands are enlarged, and diarrhea, bronchitis and a rash may be noted. Recovery occurs in 3 to 4 weeks, though in some cases the chronic stage may develop. The fever and edema subside while the lymphadenopathy persists. Cardiac symptoms and abnormalities are most often seen in this stage and are due to a chronic infiltrative myocarditis. Anemia is usually present. The thyroid gland has been reported to be enlarged and many symptoms of myxedema and cretinism were earlier included as manifestations of Chagas's disease. These complications are now thought to be manifestations of endemic goiter which is prevalent in Brazil.

Symptoms of nervous system involvement are most marked during the acute phase and sometimes form the most striking part of the clinical picture. Convulsions are common and are usually present terminally, though they may occur initially or at any time during the disease (Chagas (271)). Mazza, Friere and Salica (272) stressed the early appearance of symptoms of meningo-encephalitis in their cases, all under one year of age. In 3 of their patients, the onset was marked by the sudden appearance of a series of convulsive seizures, with the fever and adenitis appearing later. In another case continuous right-sided tremors associated with nuchal rigidity appeared on the fifth day of the illness. In still another case, the illness appeared abruptly with fever, edema of one eye and restlessness. On the sixth day the edema subsided but returned on the 15th day, accompanied by convulsions which lasted for three days before eventual recovery.

In the chronic phase there have been described many nervous symptoms such as mental retardation, apathy, speech disorders and idiocy, but these may well have been due to an associated cretinism rather than to trypanosomiasis. Paralyses, locomotory disorders, incoordination, convulsions and coma have been noted in dogs experimentally infected (Villela and Torres (273)).

Parasitic infiltration and various inflammatory changes have been found scattered throughout the brain and meninges. Inflammatory nodules surrounding parasitized cells are most commonly seen (Vianna (274), Torres and Villaca (275), Mazza, et al. (272)).

LEISHMANIASIS

Leishmaniasis is an infection caused by the flagellate protozoa of the genus Leishmania. It is made up of two forms, a visceral form known as kala-azar or infantile leishmaniasis and a cutaneous form known as tropical or oriental sore.

Visceral leishmaniasis or kala-azar is caused by Leishmania donovani and is probably spread by the sandfly. It is found in Africa, and the Mediterranean area of Europe and Asia, and is extremely frequent in India, China and Manchuria. The dog may be the principle animal reservoir in certain localities. The organism is a small round oval parasite found chiefly in the reticulo-endothelial cell or the tissue macrophage. It multiples within the cell of the host, replacing the entire cell which ultimately becomes destroyed, liberating the parasites.

The incubation period of kala-azar is from 2 to 4 months. The onset may be sudden or gradual and is ushered in with such symptoms as fever, chills, vertigo, headache, malaise, abdominal pain, nausea and vomiting. The temperature curve is irregular and often assumes the form of long irregular periods of fever alternating with periods of normal temperature. There is a progressive weight loss and a general wasting of the body. Most characteristic for this disease is the enlargement of the spleen as well as the liver. Dysentery may be present in chronic cases; anemia is usually present; and there may be hemorrhages from various parts of the body including the meninges (Strong (276)). The course of the disease is usually a chronic one, lasting several months, and death ensues in about 90 ger cent of the cases without treatment. This figure is reversed if treatment with antimony compounds is instigated.

Involvement of the nervous system is most unusual. The headaches are never severe and mental symptoms rarely occur even when the fever is high. Morpurgo (277) in 1911 described a case of infantile leishmaniasia with convulsions and meningeal symptoms. Valleteau de Mouillac and his co-workers (278) described a case of infantile leishmaniasia in which the child during treatment developed vomiting, headache and nuchal rigidity. The authors felt that the meningitis was caused by the leishmaniasia and was not a complication of the treatment. Many authors have observed paralyses or pareses in the course of spontaneous or experimental canine leishmaniasia.

No significant pathological changes in the brain have been observed in human cases (LaCava (279), Christophers (280)).

RELAPSING FEVER

Relapsing fever includes a group of spirochaetal infections which are widely distributed throughout the world and which are transmitted to many by ticks and the body louse. Some of the more common spirochaetes producing the disease are S. recurrentis (European), S. duttoni (Central African) and S. novyi (American). At the present time it is thought that these species are but varieties of one species of spirochaete (S. recurrentis). In general, the European, Indian, Chinese and West African infections are louse borne while the Central African and American forms are transmitted by ticks. In Africa, relapsing fever ranks next to malaria and sleeping sickness in prevalence and in recent years endemic centers have been reported from Texas (Kemp, et al. (281)) and California (Wheeler (282)).

Clinically the disease is characterized by the sudden onset of an acute febrile attack lasting 4 or 5 days and terminating by crisis. The rapid rise in temperature is accompanied by headaches, dizziness, general body pains, vomiting and bronchial symptoms. Jaundice may be present. After the first attack there is an afebrile and symptomless period of 4 to 8 days, followed by a similar but usually milder episode. In the European type there are usually 2 to 3 paroxysms while in the African type there may be as many as 10 relapses. Neurological complications are most frequent in the tick born infections and usually occur during the second or third paroxysm or later. The frequency of such cerebral involvement is difficult to compute and has varied from 4.5 per cent of cases (Adler, et al. (283)) to 20 per cent (Cooper (284), Scott (285)). Experimentally it has been recognized for years that the spirochaete of relapsing fever possesses a specific neurotropism (Velu et al. (286), Mathis and Durieux (287), Levaditi et al. (288), Levaditi and Anderson (289), Lagrange (290)). Heronimus (291) and Prigge (292) felt that the brain was always infected in this disease. Bonnin and Jeansotte (293) in an extensive review showed that latent residual infections in experimental relapsing fever selects only the brain, the organisms disappearing from the other tissues. A similar suggestion of the susceptibility of the nervous system has been seen in man. As early as 1907 Souli found the spirochetes more frequent in the spinal fluid than in the blood. Hawking (294) examined the spinal fluid in 12 cases of East African relapsing fever (S. duttoni) and while no parasites were found on direct examination, in 5 cases the spinal fluid was infective for mice and in 3 cases clinical evidence of meningitis was present. Lodewyckz (295) noted a lymphocytosis in the spinal fluid in 19 of 27 cases and spirochetes were found in 3 cases. The meningeal symptoms were most marked and constant in the relapses.

Clinically the most common neurological complaint is intense headache often occipital in distribution. The headache recurs with each attack of fever and often persist for weeks after the temperature subsides (Cooper (284)). The headaches are usually accompanied by vertigo, insomnia and in severe cases by delirium. Meningeal involvement is probably the most common neurological complication in relapsing fever (Liégeois et al. (296), Lafforgue (297), Scott

(285), Stones (298), Adcock (299)). Cooper (284), reported meningeal symptoms in 20 per cent of his patients. This type of involvement begins 3 weeks or more after the onset of the fever and is characterized by headaches, photophobia, stiff neck and a positive Kernig's sign. In the more severe cases the patients become restless and irritable and may develop a delirium. Spinal fluid studies show a clear fluid, moderately increased pressure and a definite pleocytosis. Scott (285) reported a variation of from 15 to 2200 cells per c.c. of which 78 to 100 per cent were lymphocytes. The total protein is slightly elevated. Only occasionally are the organisms found in a direct examination, though the fluid may be infective in mice. May (300) found numerous spirochaetes in the spinal fluid in a fatal case where all blood smears were negative. Generally, the prognosis with meningitic symptoms is good and most cases recover. Glück (301) described a case in which marked symptoms of a meningo-encephalitis persisted for five weeks.

Symptoms of an encephalitic involvement have also been reported (Vialatte (302), Liégeois, et al. (296), Scott (285)). The patient described by Vialatte showed headaches, vertigo, dysarthria, asynergia in ocular movements and marked incoördination. Intelligence was preserved. Liégeois and his associates (296) observed a case that developed definite choked discs accompanied by paresis of the right upper limb and a positive Romberg sign. Scott also reported a case with a right hemiparesis. Charters (303) described a patient with delirium and spasmodic movements of the arm.

Involvement of the cranial nerves is occasionally seen. Cooper (284) observed a facial palsy in 7 out of 60 patients. Kemp, et al. (304) noted partial facial paralysis in 2 of 258 cases, while Taft and Pike (305) noted seventh nerve paralysis in 5 of 11 cases. This finding appears later in the disease, usually after the second or third paroxysm. Scott (285) reported isolated involvement of the motor part of the 5th cranial nerve, a right abducens palsy and diplopia. Wolff (306) noted a mild myelitis manifested by motor and sensory changes in the legs in 2 of 134 cases, while Charters (303) reported a neuritis manifested by neuralgic pains and local hyperesthesias in 4 of 32 cases during convalescence.

Occasionally the illness is quite fulminating. Such patients may show marked agitation with delirium. Coma and death may follow in a few days. Terminal convulsions were seen in 2 such cases in the series reported by Wolff (306). Recovery from relapsing fever is often prolonged. Kemp, et al. (304) noted that muscular asthenia appeared to be a prominent and stubborn condition following convalescence. Taft and Pike (305) also emphasize the prolonged course and long convalescence in their cases. The patients had profound asthenia, were depressed and had frequent headaches and backaches.

Pathological changes in the nervous system are few despite the neurotropism of the organism. A leptomeningitis has been observed with extensive degeneration of the ganglion cells in the cerebral cortex. Spirochaetes were found throughout the brain within the glial cells and the cortical neurons and the basal nuclei (Belezky and Umanskaja (307)).

RAT BITE FEVER

Rat bite fever is an acute infectious disease characterized by recurrent episodes of fever, an inflammatory reaction at the site of the bite with regional lymphangitis, an exanthem and various neurologic symptoms. It is caused by Spirochaeta morsus-muris (Spirillum minus) and transmitted usually by the bite of a rat, occasionally by bites of cats, dogs and other animals (Ripley and Van Sant (308)). The disease is common in the Orient and is endemic in Japan where the mortality rate in untreated patients is 10 per cent. Cases have recently been described from many parts of the world, and 125 cases were reported in the United States through 1940 (Brown and Nunemaker (309)). In these there were no deaths.

For a short time, rate bite fever because of its relapsing nature and its complete control by arsenicals was used for the treatment of syphilitic paresis. Solomon and co-workers (310) instituted this form of treatment in 1926 and since then over 100 cases of rat bite fever have been artificially produced by the inoculation of Spirochaeta morsus-muris (Bayne-Jones (311), Hershfield et al. (312), Teitelbaum (313)). However, this form of treatment has been abandoned because of the 10 per cent mortality with some strains of the organism and because of the high incidence of complications (arthritis, myositis, convulsions, etc.).

Clinically the disease has an incubation period of from 10 to 20 days during which the rat bite heals. The onset of symptoms is rather sudden with headache, malaise, muscle pains, nerve trunk tenderness, an inflammation at the original bite and associated lymphadenopathy and lymphangitis. A fever develops and remains for 4 to 5 days, usually accompanied by a rash. The symptoms disappear with the fall in fever only to appear again in 4 to 5 days with the recurrence of the febrile episode. Usually there are from 3 to 10 paroxysms which, as the disease progresses, decrease in severity and occur at greater intervals.

Neuropsychiatric symptoms comprise some of the most common complaints and invariably appear at the height of the first few paroxysms of fever. In the most severe cases the patients complain of headache, vertigo, tinnitus, nausea and vomiting and blurring of vision (Arkin (314), Gilkey and Dennie (315), McDermott (316)). These symptoms usually subside with the fall of the temperature. In some of the more severe cases the neurological involvement may be more extensive and lasting. Cranial nerve lesions may produce dysphagias, aphonias, amaurosis, deafness and papilledema (Ebert and Hesse (317), Rosdolsky (318), Millot-Carpentier (319)). Ebert and Hesse's patient developed a left-sided blindness and deafness and a polyneuritis 3 days after a bite on the left cheek. Recovery followed treatment with salvarsan. Motor disturbances are often quite definite and may persist as a permanent sequel. The motor symptoms include muscular twitchings, convulsions, hemiplegias, pareses and even muscular atrophies. Rubino (320) reported a case with fibrillary twitchings in the trunk muscles in a 12 year old boy, while convulsions have been observed by Drgisic and Kolundjerski (321) and Morgan (322). In one of these cases the seizures were unilateral and terminated fatally in a few days. Motor

weakness or paralysis is an uncommon complication (Banker (323), Yanajiro (324)). In the latter's case a left-sided hemiplegia associated with unconsciousness appeared during the 5th paroxysm and 1 year later the patient still revealed some weakness in his left hand.

Sensory involvement usually occurs in the most severe cases and varies from paresthesias to areas of complete anesthesia, particularly in the extremities. Patches of hyperesthesia may occur anywhere on the body (McDermott (316)). Muscle tenderness is practically a constant symptom with severe pain along the nerve trunks (Crohn (325)). Often these painful limbs are associated with a motor weakness of a flaccid type resulting in a mild wasting of the involved extremity (Crohn (325)). Rosdolsky (318) observed a patient who 1 week after the bite developed headache, fever and hypesthesia over the entire left face and a papilledema. Recovery followed after treatment with arsenicals.

Occasionally the illness may be severe with encephalitic symptoms dominating the clinical picture. The patients complain of severe pain in the region of the bite along with vertigo, great anxiety, severe headaches, rapid pulse, sensory or motor disturbances, insomnia, delirium and hallucinations followed after a few days by stupor, coma and death. The delirium is usually severe and if prolonged invariably results fatally (Banker (323), Ishiwara et al. (326)). Meningeal involvement is uncommon but has been reported (Dembo et al. (327)).

Pathological studies of the central nervous system in rat bite fever are few. Drgisic and Koludjerski (321) found a necrotic softened area in the corpus callosum of a 14 months old child who had unilateral convulsive siezures before death.

AMEBIASIS

Amebic dysentery is an intestinal infection with the pathogenic ameba, Endamoeba histolytica. It is world-wide in distribution and though most frequent in the tropics, it is also common in the temperature zones. According to Craig (328), 5 to 10 per cent of the inhabitants in the United States have amebiasis. Endamoeba histolytica primarily infects the intestine, reaching the bowel through food and water contaminated with fecal material containing amebic cysts. Symptoms of acute and chronic dysentery result, or a carrier state may develop with few or no symptoms. From the intestinal lesions the amebae may metastasize to the liver and rarely to other organs, such as the brain where they raise a primary purulent encephalitis or a brain abscess. It has been estimated that liver abscesses occur in from 33 to 51 per cent of persons with amebic dysentery that come to autopsy, while only 3 per cent of these show brain involvement (Clark (329), Gehlen (330), Kartulis (331)). About 65 cases of amebic brain abscess have been reported in the literature, and in only 5 cases did the brain involvement occur without liver abscesses or other associated findings of amebiasis (Kartulis (331), Putney and Baker (332), Stein and Kazan (333)).

The clinical manifestations of cerebral amebiasis include the symptoms and signs of a diffuse suppurative meningo-encephalitis and the focal signs of an abscess. Generally the cerebral symptoms are preceded by signs of liver or

chest involvement, often following operations for such complications. Headaches seem to be the most outstanding symptom. They are usually progressive and extremely severe and soon become associated with signs and symptoms of increased intracranial pressure such as nausea, vomiting, vertigo, impairment of consciousness and choked disc. The patient shows varying degrees of drowsiness, lethargy, stupor or coma. In some cases, following the drainage of a suppurative hepatitis or lung abscess, the patient dramatically develops a severe delirium with stupor (Halpert and Ashley (334)) or generalized convulsion (Stein and Kazan (333)). Usually after the onset of such severe symptomatology the course is rapidly downhill with death ensuing in a few days. Focal symptoms and signs depend on the localization of the infective process. Jacksonian seizures, aphasias (Kartulis (331)), hemiplegias (Putney and Baker (332)), diplopia, strabismus, and many other focal symptoms have been reported.

Usually toxic symptoms are not prominent and the temperature, although elevated, remains fairly moderate. Meningeal signs and symptoms as a rule are not a prominent part of the clinical picture. In some cases, however, the abscess does adjoin the surface of the brain resulting in definite meningeal involvement (Stein and Kazan (333), Halpert and Ashley (334)). In such cases the patients show a definite Kernig and Brudzinski sign as well as opisthotonos. The spinal fluid is cloudy and may contain as many as 6600 cells with 68 per cent polymorphonuclears (Stein and Kazan (333)). These meningeal cases soon pass into coma and terminate fatally in a very few days.

Aside from the specific indication of a primary involvement, many cases of chronic amebiasis reveal symptoms indicative of a nonspecific effect upon the nervous system. Covey, Rogers and Underwood (335) studied 100 cases of amebiasis and observed 21 with headaches and vertigo, 10 with nervousness, 3 with syncope and 2 with tremor. These could well be general somatic complaints secondary to the debilitation of a chronic disease. Wright (336) in a study of 25 cases emphasized the neuropsychiatric symptoms. He found that most patients with intestinal amebiasis had a depression, inability to concentrate, headaches, insomnia and nervousness resulting in a state resembling a severe psychoneurosis. Craig stated that a number of subjective symptoms exist in patients who are carriers of amebiasis. These are headaches, aching pains in the arms and legs, somnolence, poor memory, irritability, backache and mental depression.

ANIMAL PARASITES (HELMINTHS)

Ascariasis. Ascariasis is caused by infection with the round worm Ascaris lumbricoides, the most common helminth parasite of man. It is world-wide in its distribution but is more prevalent and severe in the tropics due to environmental conditions and sanitation practices. After ingestion, the eggs hatch in the small intestine, the larvae migrate through the portal system to the lungs, are coughed up and swallowed reaching again the intestine where they develop into adults. Symptoms of ascaris pneumonia may occur during the larvae migration. The adult worms may cause little annoyance or may produce a

arthropod vector and the worms are transmitted from man to man by various species of mosquitoes and biting flies. The most common species are Wuchereria bancrofti, Loa loa, Dipetalonema perstans and Onchocerca volvulus. All species have a wide distribution in the tropical and subtropical countries with considerable variation in prevalence in local areas.

Infection with Wuchereria bancrofti, commonly called filariasis, is the most widespread of all the filarial infections. In this disease the adult worms are found chiefly in the lymphatics. The incubation period is about a year and the infection may remain entirely asymptomatic or may be evidenced by recurring attacks of lymphangitis. The chronic stages occur through lymphatic obstruction with resulting dilated lymphatics, enlarged lymph glands, lymphoceles, hydroceles and elephantiases. The circulating microfilariae are apparently symptomless.

Several investigators feel, however, that nervous system symptoms occasionally seen in filariasis are due to the presence of microfilariae in the brain. Mya (376) described a case of a patient admitted to the hospital for sudden loss of consciousness four hours previously. The next day the patient was semiconscious and developed a right hemiplegia and died sometime later. The only positive finding elicited was the presence of microfilariae in the spinal fluid. Manson (377) stated that microfilariae can be found in the brain, and Anderson (379) reported a case with numerous microfilariae in the cerebral and cerebellar blood vessels. Some leucocytic infiltration was present around cerebral capillaries. Rodenwaldt (378) also found microfilariae in the cerebral capillaries, but he was unable to find any associated tissue changes.

Filariasis due to Dipetalonema perstans is characterized by the absence of consistent symptoms. The adult worms prefer the serous cavities and mesentery of the body and the microfilariae are found more often in the larger vessels than in the peripheral blood. Most writers feel that an infection with this parasite is nonpathogenic while others state it may produce symptoms similar to that seen in Wuchereria infection. Külz (380) described a case in which the patient had typical psychic and motor symptoms of sleeping sickness, but the spinal fluid contained only microfilariae. Chambon (381) reported on a case in which the cerebrospinal fluid showed both microfilariae and trypanosomes. He felt that the meninges were altered by the trypanosome infection permitting the entrance of microfilariae.

Loiasis, the form of filariasis caused by Loa loa, is distinguished by transient swellings and inflammatory phenomena in the subcutaneous tissues of the body, including the eye. It is possible in this infection as in the others for the microfilariae to lodge in the brain and cause symptoms.

The fourth filarial disease, Onchocerciasis, is characterized by subcutaneous nodule formation. The symptoms are due to the nodules and include local discomfort, inflammatory changes, erysipelas and ocular disturbances. Robles (382) found 4 of 500 patients in which the nodules had eroded both tables of the skull, with one tumor resting directly on the meninges. One case had epileptiform seizures from irritation by a tumor nodule which had penetrated the cranium.

The microfilariae can apparently give rise to symptoms in this disease as in the others. Mira (383) found microfilariae in the optic nerve following enucleation of an eye for extensive ocular onchocerciasis and Rodhain (384) found them in the meninges in one of his cases.

Schistosomiasis. Schistosomiasis includes the group of diseases caused by those species of flukes which inhabit the venous system of man in various tropical and subtropical countries. The three common species are Schistosoma haematobium, Schistosoma mansoni and Schistosoma japonicum. The first, Schistosoma haematobium, is endemic throughout Africa and the Near East. It usually localizes in veins of the pelvic plexus, particularly in the wall of the bladder where the extruded ova cause symptoms of hematuria, dysuria, cystitis and other urinary difficulties. Schistosoma mansoni is found in South America and the Antilles in addition to the Nile Valley and other parts of Africa. It commonly localizes in the portal system and gives rise to chronic dysentery and various intestinal symptoms. Ova are found in great numbers in the liver, causing cirrhosis with splenomegaly. Schistosoma japonicum is found in the Far East in China, Japan, Formosa, Celibes and the Philippines. It localizes in the portal system as does Schistosoma mansoni and similar symptoms are produced though they are often of a more severe nature.

Part of the life cycle of the parasite is spent in snails and the human infection is acquired by contact with the free swimming forms in water. The pathological lesions are largely caused by the eggs which are passed by the female worms into the venous system. The infection is a chronic one and parasites may live in the body for many years. In some areas the disease is severe and a large percentage of the population is infected. Persons exposed to repeated infections are most likely to develop chronic sequellae.

There are two ways in which the central nervous system is affected in Schistosomiasis according to Greenfield and Pritchard (385). In one, lesions are caused by the circulating ova which get past the liver and lung barrier and act as emboli in the brain. In the other, the circulating larvae develop into adults in the veins of the brain and ova are extruded in situ. This latter possibility is suggested on the basis of the large number of eggs circumscribed within the lesions they describe. In the first of two cases reported by Greenfield and Pritchard (385) the symptoms consisted of epileptiform seizures, hemianopia, scotomata, aphasia, clumsiness of the right hand and difficulty in thinking. The findings included injected optic discs, slight right facial weakness, increased reflexes on the right and a spinal fluid with 79 cells—93 per cent lymphocytes. A tumor was removed from just beneath the surface of the brain in the left parietal region which proved to be a granuloma containing eggs of Schistosoma japonicum. Their second case had persistant headaches and vomiting, scotomata, a field defect, difficulty with speech and impaired finer movements of the right hand. A large tumor of similar nature was removed from the left parieto-occipital region.

Other authors have felt that the nervous system lesions were due to embolic ova. Tsunoda and Shinamura (386) in 1906 described a case in which a dis-

turbance in speech and tremors of the arms and legs were noted for several months. Later the patient suffered from headaches, memory loss, reflex changes, epileptiform seizures and a right hemiplegia. Several lesions containing schistosome ova were found in the brain and spinal cord. Edgar (387) observed a patient in whom convulsions and symptoms similar to the above case were present. A typical tumor containing eggs of Schistosoma japonicum was removed at operation. Vitug, Cruz and Bautista (388) described a similar case with a sudden onset of convulsions. Ferguson (389) recorded a case in which the clinical symptoms resembled multiple sclerosis, and post-mortem examination showed eggs in the spinal cord. The syndrome of transverse myelitis due to schistosoma ova has been noted by several authors (Ferguson (390), Müller and Stender (391), Day and Kenaway (392), Bayoumi (393), Espin (394)).

Recently there have been several reports of symptoms of acute schistosomiasis in military personnel following the invasion of Leyte in 1944 (Thomas and Gage (395), Hunt (396), Faust et al. (397)). Neurological manifestations were noted in 3 of 42 cases (Thomas and Gage (395)), and consisted of weakness of the arms and spasticity of the legs with increased deep reflexes. One patient was disoriented on admission and another was admitted in coma. Faust et al. (397) recorded 3 additional cases with neurological manifestations. One patient developed a left sided weakness with spasticity 11 days after the onset of acute symptoms. A second case had evidence of lesions in both right and left motor cortex six weeks after exposure. A third patient had marked weakness on the left side with numbness of the left face and hand. He had a Jacksonian seizure 6 months after exposure and one month after the first appearance of his neurological symptoms. Hunt (396) described a similar picture and noted the presence of scattered paresthesias during the acute phase and marked weakness and fatigue as residual symptoms. The neurological symptoms are interpreted as being due to embolic ova (Faust et al. (397)).

Paragonimiasis. Paragonimiasis is caused by an infection with the fluke Paragonimus westermani which inhabits the tissues of the lungs of man and various mammals. It is present throughout the Orient and has also been recorded from parts of Africa and South America. In some districts of Japan 40 to 50 per cent of the population is infected. Two intermediate hosts are required in the life cycle, snails and then crabs and crayfish containing encysted larvae. After ingestion, the larvae migrate through the intestinal wall to the lungs where they develop into adults.

Not infrequently the larvae and young adults migrate and develop in other tissues, including the brain. Cysts similar to those found in the lungs develop in the intracranial cavity and symptoms of an intracranial neoplasm result. The first of a number of such cases was described by Otani in 1887. His patient had lung fluke infection complicated by epileptiform seizures, apathy and confusion. An autopsy revealed 2 masses of communicating cysts within the brain, containing live flukes. Yamagawa (398) reported a similar case with convulsions and hemiparesis of two years duration. Taniguchi (399) described a case of a 17 year old girl with symptoms of epilepsy, chorea and athetosis, weakness of the

left side and intellectual deterioration. Musgrave (400) recorded a case with convulsive seizures. Pathological studies in all these cases showed cysts with groups of fluke eggs. In 1921 Kawamura and Yamaguchi (401) reviewed 38 cases of cerebral paragonemiasis in the literature and added 37 of their own. They stressed the occurrence of epileptiform seizures, transient paralyses and other neurological disturbances in children. One case they examined pathologically had a 9 year history of convulsions and deterioration. Kimura (402) reported on a case in which mental peculiarities and hallucinations were noted before death. Autopsy revealed many cysts throughout the brain with atrophy of the occipital lobes.

BIBLIOGRAPHY

1. Chalmers, W. S. and Baker, A. B.: Arch. Path. 41: 66, 1946.
2. Jacob, A., Fialho, A. and Villela, E. L.: Deutsche Ztschr. f. Nervenh. 111: 111, 1929.
3. Stevenson, L. S.: Arch. Path. 27: 249, 1939.
4. Nicolau, S., Mathis, M. and Baffet, O.: Bull. Soc. path. exot. 30: 615, 1937.
5. Goonpasture, E. W.: Am. J. Path. 8: 137, 1932.
6. Lloyd, W. and Penna, H. A.: Am. J. Trop. Med. 13: 1, 1933.
7. Findlay, G. M. and Stern, R. O.: J. Path. & Bact. 40: 311, 1935.
8. Sorel, F.: Bull. Office internat. d'Hyg. Pub. 28: 1325, 1936.
9. Fox, J. P., Lennette, E. H., Manso, C. and Souza-Aguiar, J. R.: Am. J. Hyg. 36: 117, 1942.
10. Jungman, P.: Klin. Wchnschr. 8: 14, 1929.
11. Hoffmann, W. H.: Deutsche med. Wchnschr. 52: 1729, 1926.
12. Berry, G. P. and Kitchen, S. F.: Am. J. Trop. Med. 11: 365, 1931.
13. Aitken, A. B., Connal, A., Gray, G. H. and Smith, E. C.: Tr. Roy. Soc. Trop. Med. & Hyg. 20: 166, 1926.
14. Nicolson, W. P.: Tr. Med. Assn. Georgia 35: 130, 1884.
15. Findlay, G. M. and Stern, R. O.: J. Path. & Bact. 41: 431, 1935.
16. Ristol, J.: Med. mil espan. Madrid 3: 257, 1897.
17. Ferandez, I. S.: Arch. Opth. 10: 440, 1881.
18. Stephanopoulo, G. J. and Mollaret, P.: Bull. et mém. Soc. méd. d. hôp. de Paris 50: 1463, 1934.
19. Saunders, J. M.: Eclectic M. J. Cincinnati 2: 352, 1856.
20. Perez Aranibar, A. E.: Crón. méd., Lima 1: 210, 1884.
21. Le Gac, P.: Bull. Soc. path. exot. 22: 743, 1929.
22. Hanson, H.: J. A. M. A. 66: 548, 1926.
23. Lacorte, J. G. and Villela, G. C.: Compt. rend. Soc. de biol. 99: 1663, 1928.
24. Mollaret, P. and Stephanopoulo, G. J.: Compt. rend. Soc. de biol. 117: 1101, 1934.
25. Kino, W. W.: New Orleans M. & S. J. 69: 564, 1916–1917.
26. Apostolopoulos, K. G.: München. med. Wchnschr. 77: 265, 1930.
27. Ghiannoulatos, G. P.: Rev. neurol. 38: 599, 1931.
28. Richardson, S.: Tr. Am. Ophth. Soc. 31: 450, 1933.
29. Baroy, M.: Bull. et mém. Soc. franc. d'opht. 42: 293, 1929.
30. Pamboukis, G.: Schweiz. Arch. f. Neurol. u. Psychiat. 26: 51, 1930.
31. Gill, W. D.: Arch. Ophth. 57: 628, 1928.
32. Faver, M.: J. Florida M. A. 24: 395, 1938.
33. Simmonds, J. S.: Dengue Fever, in Virus and Rickettsial Diseases, Harvard University Press, Cambridge, 1941, p. 349.
34. Tsiminakis, K.: Wien. klin. Wchnschr. 43, part 2: 755, 1930.
35. Stewart, F. H.: U. S. Nav. M. Bull. 42: 1233, 1944.
36. Kisner, P. and Lisansky, E. T.: Ann. Int. Med. 20: 41, 1944.

37. Kaplan, A. and Lindgren, A.: U. S. Nav. M. Bull. **45:** 506, 1945.
38. Le Roy, G. V. and Lindberg, H. A.: Bull. U. S. Army Med. Dept. No. **27:** 92, 1944.
39. Catsaras, J.: Arch. f. Schiffs- u. Tropen-Hyg. **35:** 278, 1931.
40. Melissinos, J.: Arch. f. Schiffs- u. Tropen-Hyg. **41:** 321, 1937.
41. Gerhard, W. W.: Am. J. M. Sc. **20:** 289, 1837.
42. Murchison, C.: A Treatise on the Continued Fevers of Great Britain, London, Longmans, Green and Company, 1873.
43. Curschmann, H., in Nothnagel, H.: Encyclopedia of Practical Medicine, Philadelphia, W. B. Saunders and Company, 1901, vol. 1, p. 475.
44. Hampeln, P.: Deutsches Arch. f. Klin. Med. **26:** 238, 1880.
45. Hirschberg, N.: Abh. Neurol. psychiatr. Psychol. **66:** 1, 1932.
46. Devaux, A.: Lancet **1:** 567, 1919.
47. Rabinowitsch, J. S.: Ztschr. f. d. ges. Neurol. u. Psychiat. **115:** 34, 1928.
48. Arnold, V.: Wein. klin. Wchnschr. **32:** 893, 1919.
49. Braunstein, E. P.: Arch. f. Ophth. **113:** 359, 1924.
50. Chung, H.: Chinese M. J. **50:** 1427, 1936.
51. Feldman, P. M.: Arch. f. Psychiat. **77:** 357, 1926.
52. Sturm, A.: Klin. Wchnschr. **21:** 899, 1942.
53. von Baeyer, W.: Ztschr. f. d. ges. Neurol. u. Psychiat. **175:** 225, 1942.
54. Skliar, N.: Monatschr. f. Psychiat. u. Neurol. **52:** 21, 1922.
55. Munk, F.: Med. Klin. **36:** 452, 1940.
56. Stockert, F. G.: Deutsche Med. Wchnschr. **69:** 506, 1944.
57. Grodski, A. B.: München. med. Wchnschr. **76:** 709, 1929.
58. Wells, H. G. and Perkins, R. G.: J. A. M. A. **70:** 743, 1918.
59. Lippmann, H.: Deutsche Med. Wchnschr. **44:** 1425, 1918.
60. Danielopolu, D.: Le typhus exanthématique, Bucharest, Inst. d Arts Graph. 1919.
61. Heilig, G.: München. med. Wchnschr. **65:** 1434, 1918.
62. Heuyer, G.: Compt. rend. Soc. de biol. **82:** 729, 1919.
63. Kritschewsky, I. L. and Autonomow, W.: Ztschr. f. d. ges. Neurol. u. Psychiat. **85:** 78, 1923.
64. Selman, D.: Bull. U. S. Army M. Dept. No. **86:** 121, 1945.
65. Wolbach, S. B., Todd, J. L. and Palfrey, F. W.: The Etiology and Pathology of Typhus, Cambridge, Mass., Harvard University Press, 1922.
66. Ceelen, W.: Klin. Wchnschr. **53:** 530, 1916.
67. Davidowsky, J. W.: Ergebn. d. allg. Path. u. path. Anat. **20:** part 2: 571, 1924.
68. Maxcy, K. F.: Pub. Health Rep. **41:** 1213, 1926.
69. Rumreich, A. S.: J. A. M. A. **100:** 331, 1933.
70. Kemp, H. A.: Am. J. Trop. Med. **19:** 109, 1939.
71. Miller, E. S. and Beeson, P. B.: Medicine **25:** 1, 1946.
72. Mooser, H.: J. Infect. Dis. **43:** 241, 1928.
73. Dyer, R. E., Ceder, E. T., Lillie, R. D., Rumreich, A. and Badger, L. F.: Pub. Health Rep. **46:** 2481, 1931.
74. Rumreich, A., Dyer, R. E. and Badger, L. F.: Pub. Health Rep. **46:** 470, 1931.
75. Wolbach, S. B.: J. Med. Res. **41:** 1, 1919.
76. Carey, L. S. and Duncan, G. G.: J. A. M. A. **110:** 175, 1938.
77. Cohen, M. H.: J. A. M. A. **115:** 1441, 1940.
78. Crutcher, J. S.: South. M. J. **26:** 415, 1933.
79. Hutton, J. G.: J. A. M. A. **117:** 413, 1941.
80. Smith, E. B. and Rheinhard, E. H.: J. Missouri M. A. **40:** 166, 1943.
81. Baker, G. E.: Ann. Int. Med. **17:** 247, 1942.
82. Reading, G. and Klint, H.: Am. J. Trop. Med. **23:** 445, 1943.
83. Parker, R. R.: J. A. M. A. **110:** 1273, 1938.
84. Ong, H. A. and Raffetto, J. F.: J. Pediat. **17:** 647, 1940.
85. Bennett, T. B.: M. Bull. Vet. Admin. **17:** 425, 1941.

86. Palatucci, O. A. and Maragoni, B. A.: Bull. U. S. Army M. Dept. No. 79: 116, 1944.
87. Lillie, R. D.: Pub. Health Rep. 46: 2840, 1931.
88. Hassin, G. B.: Arch. Neurol. and Psychiat. 44: 1290, 1940.
89. Dias, E. and Martins, A. V.: Am. J. Trop. Med. 19: 103, 1939.
90. Piza, J, T., Meyer, J. R. and Gomes, L. S.: Typho Exanthematico do Sao Paulo, Sao Paulo, Sociedade Impressore Paulista, 1932.
91. Toppino, N. H., Heilig, R. and Naidu, V. R.: Pub. Health Rep. 58: 1208, 1943.
92. Augier, P. and Durandy, P.: Bull et mém. Soc. méd. d. hôp de Paris 52: 1545, 1936.
93. Augier, P. and Cossa, P.: Bull. et mém. Soc. méd. d. hôp. de Paris 51: 432, 1935.
94. Williams, S. W., Sinclair, A. J. M. and Jackson, A. V.: M. J. Australia 2: 525, 1944.
95. Greenfield, I.: Arn. Int. Med. 24: 192, 1946.
96. Machella, T. E. and Forrester, I. S.: Am. J. M. Sc. 210: 38, 1945.
97. Lipman, B. L., Byron, R. A. and Casey, A. V.: Bull. U. S. Army M. Dept. 72: 63, 1944.
98. Lewthwaite, R. and Savoor, S. R.: Lancet 1: 255, 1940.
99. Heaslip, W. G.: M. J. Australia 1: 380, 1941.
100. Hay, C. P.: Roy. Nav. M. Serv. 30: 127, 1944.
101. Scheie, H. G.: Bull. U. S. Army M. Dept. 5: 423, 1946.
102. Lewthwaite, R.: J. Path. & Bact. 42: 23, 1936.
103. Kouwenaar, W.: Beneesk. tijdschr. v. Nederl.-Indië 80: 1119, 1940.
104. Corbett, A. J.: Bull. U. S. Army M. Dept. No. 70: 34, 1943.
105. Derrick, E. H.: M. J. Australia 2: 281, 1937.
106. Dyer, R. E.: J. A. M. A. 122: 331, 1943.
107. Morrissey, G. C. and Derrick, E. H.: M. J. Australia 2: 214, 1945.
108. Lillie, R. D.: Pub. Health Rep. 57: 296, 1942.
109. Camargo, L. P.: Fac. do med. Bogotá 9: 160, 1940.
110. Montalván and Moral, cited by Strono, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, Philadelphia, The Blakiston Company, 1943, vol. 2, p. 1004.
111. Barton, A. L.: Crón. med., Lima 18: 193, 1902.
112. Carrion, D.: Cited by Lastres (113).
113. Lastres, J. B.: Rev. méd. peruana. 6: 1690, 1934.
114. Monge, C. and Mackehenie, D.: Rev. méd. peruana. 4: 523, 1932.
115. Olaechea, M. G.: Crón. méd., Lima, Nov. 1890.
116. Quiroga, J. M. and Mena, F.: Crón. méd., Lima, Dec. 1889.
117. Morales, A. L.: Rev. méd. peruana. 5: 646, 1933.
118. Méndez, M. and Angelos Quintanos, P.: Rev. neurol. e psychiat. de Sao Paulo 3: 88, 1940.
119. Lastres, J. B.: Dig. Neurol. and Psychiat. Series 14, May, 1946.
120. Mackehenie, D. and Alzamora, V. V.: J. Neuro-psiquiát. panam. 2: 166, 1940.
121. Alexander, L. and Wu, T. T.: Chinese M. J. 48: 1, 1934.
122. Olitsky and Klieler, in Strono, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, Philadelphia, The Blakiston Company, 1943, vol. 1, page 551.
123. Zellweger, H.: Praxis 32: 707, 1943.
124. von Gröer, F.: Ztschr. f. Kinderh. 21: 220, 1919.
125. Deshmukh, P. L.: Indian M. Gaz. 66: 83, 1931.
126. Hofstede, G. W.: Psychiat. en neurol. bl. 32: 394, 1928.
127. Müller-Deham, A.: Wien. med. Wchnschr. 65: 654, 1915.
128. Singer, K.: Monatschr. f. Psychiat. u. Nourol. 41: 245, 1917.
129. Kamar: Acta Univ. Szeged. 1940.
130. Burnet, J. B.: M. & Surg. Reporter 16: 47, 1867.
131. Comby, J.: Arch. de méd. d. enf. 10: 577, 1907.
132. Menzel, W.: Deutsche Ztschr. f. Nervenh. 126: 265, 1932.
133. Lenhartz, H.: Klin. Wchnschr. 21: 312, 330, 1883.
134. Buttenwieser, S.: München. med. Wchnschr. 67: 1472, 1920.

236. Kraepelin, E.: Arch. f. Psychiat. 11: 164, 1881.
237. Pasmanik, D.: Wien. med. Wchnschr. 47: 565, 1897.
238. Parot, A. and Gutmann, R. A.: Paris méd. 24: 518, 1917.
239. Forrester, A. T. W.: Lancet 1: 16, 1920.
240. Berlin, B. M.: Molotov med. Inst. 21: 247, 1942.
241. Gehrenstein, S. S.: Vrach. Gaz. 13: 919, 1906.
242. Gordon, H. H., Lippincott, S. W., Marble, A., Ball, A. L., Ellerbrook, L. D. and Blass, W. W.: Arch. Int. Med. 75: 159, 1945.
243. Bispham, W. N.: Am. J. Trop. Med. 21: 455, 1941.
244. Pope, C.: Boston M. and Surg. J. 170: 193, 1914.
245. Atkinson, J. F.: Indian M. Rec. 33: 177, 1913.
246. Musgrave, W. E.: Bull. Manila M. Soc. 3: 28, 1911.
247. Tumulty, P. A., Nichols, E., Singewald, M. L., and Lidz, T.: Medicine 25: 17, 1946.
248. Zeligs, M. A.: J. A. M. A. 129: 796, 1945.
249. Van Zyl, W. J. and Gear, J.: South African M. J. 15: 278, 1941.
250. Bertrand, I., Bablet, J., and Sicé, A.: Ann. Inst. Pasteur 54: 91, 1935.
251. de Savitsch, E., and Freeman, W.: Med. Ann. Dist. Columbia 8: 231, 1939.
252. Mott, F. W.: Roy. Soc. Rep. Sleeping Sickness Comm. VII 15: 1, 1906.
253. Sicé, A. and Leger, M.: Bull. Soc. path. exot. 24: 828, 1931.
254. Sicé, A.: Bull. Soc. path. exot. 23: 77, 222, 307, 1930.
255. Bertrand, I.: Bull. Soc. path. exot. 27: 522, 1934.
256. Duren, A. and van den Branden, F.: Ann. Soc. belge de méd. trop. 14: 437, 1934.
257. Low, G. C. and Castellani, A.: Roy. Soc. Rep. Sleeping Sickness Comm. II, 5: 14, 1903.
258. Sicé, A. and Moreau, P.: Bull. Soc. path. exot. 28: 722, 1935.
259. Vix, W.: Arch. f. Psychiat. 50: 1, 1912.
260. Fain, A. M.: Rec. trav. Sc. Med. Congo belge p. 156: Jan. 1945.
261. Sicé, A., Robin, C. and Oberle, G.: Bull. Soc. path. exot. 32: 649, 1942.
262. Pinard, M., Brumpt, L. and Raymondeau, M.: Bull. et mém. Soc. méd. d. hôp. de Paris 55: 324, 1939.
263. Moustardier, G.: Bull. Soc. path. exot. 29: 435, 1936.
264. Bertrand, Y.: Bull. Soc. path. exot. 28: 606, 1935.
265. Darré, H., Mollaret, P., Tanguy, Y. and Mercier, P.: Bull. Soc. path. exot. 30: 159, 1937.
266. Christy, C.: Roy. Soc. Rep. Sleeping Sickness Comm. III, 6: 1, 1903.
267. Kirschbaum, W.: Ztschr. f. d. ges. Neurol. u. Psychiat. 132: 269, 1931.
268. Barlovatz, A.: Ann. Trop. Med. 28: 1, 1934.
269. Sicé, A.: Bull. Soc. path. exot. 23: 582, 1930.
270. Barlovatz, A.: Bull. Soc. path. exot. 23: 1014, 1930.
271. Chagas, C.: Mem. Inst. Oswaldo Cruz 8: 5, 1916.
272. Mazza, S., Friere, R. S. and Salica, P. N.: Univ. Buenos Aires, Misión de estudios de Patologia Regional Argentina, Pub. #60, 1942.
273. Villela, E. and Torres, C. M.: Mem. Inst. Oswaldo Cruz 19: 198, 1926.
274. Vianna, C.: Mem. Inst. Oswaldo Cruz. 3: 276, 1911.
275. Torres, C. M. and Villaca, J.: Mem. Inst. Oswaldo Cruz 11: 80, 1919.
276. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, Philadelphia, The Blakiston Company, 1943, vol. I, page 268.
277. Morpurgo, L.: Arch. Inst. Pasteur, Tunis 3: 111, 1911.
278. Valleteau de Mouillac, Duliscouet, and Delacoux des Roseaux: Paris méd. 109: 241, 1938.
279. LaCava, F.: Atti de Roy. Acad. Lincei R. C. 20: 778, 1911.
280. Christophers, S. R.: Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India 8: 11, 1904.
281. Kemp, H. A., Moursund, W. H. and Wright, H. E.: Am. J. Trop. Med. 13: 425, 1933.

282. Wheeled, C. M.: Am. J. Trop. Med. 18: 431, 641, 1938.
283. Adled, S., Theodor, V. and Schrieber, H.: Ann. Trop. Med. 31: 25, 1037.
284. Cooper, E. L.: M. J. Australia 1: 035, 1942.
285. Scott, R. B.: Lancet 2: 436, 1044.
286. Velu, H., Balozet, L. and Zoltner, G.: Compt. rend. Soc. de biol. 106: 1089, 1931.
287. Mathis, C. and Durieux, C.: Bull. Soc. path. exot. 23:862, 1030.
288. Levaditi, C., Anderson, T. E., Seldie, F. R. and Schoen, R.: Bull. Acad. de méd., Paris 103: 073, 1030.
289. Levaditi, C. and Anderson, T. E.: Compt. rend. Soc. de biol. 100: 1121, 1929.
290. Laoranoe, E.: Bull. Soc. path. exot. 24: 804, 1931.
291. Heronimus, E. S.: Zentralbl. f. Bakt. 105: 394, 1928.
292. Pdigoe, D.: Deutsche med. Wchnschr. 9: 356, 1920.
293. Bonnin, H. and Jeansotte, G.: Biol. méd., Paris, 30: 121, 1940.
294. Hawkino, F.: J. Trop. Med. 44: 104, 1941.
295. Lodewyckx, A.: Ann. Soc. belge de méd. trop. 18: 487, 1938.
290. Liegeois, R., Paoès, R., Duouet, J. and Pouhin: Presse Med. 46: 531, 1038.
297. Laffodoue: Rev. de med., Paris 28: 910, 1908.
298. Stones, R. Y.: Kenya M. J. 3: 27, 1920.
299. Adcock, E. W.: West African M. J. 2: 172, 1029.
300. May, W. C. K.: Chinese M. J. 62: 142, 1944.
301. Glück, G.: Deutsche med. Wchnschr. 69: 653, 1943.
302. Vialatte, C.: Arch. Inst. Pasteur d'Algérie 4: 50, 1926.
303. Charters, A. D.: Tr. Roy. Soc. Trop. Med. & Hyg. 35: 271, 1942.
304. Kemp, H. A., Moursund, W. H. and Wright, H. E.: Am. J. Trop. Med. 15: 495, 1935.
305. Taft, W. C. and Pike, J. B.: J. A. M. A. 129: 1002, 1045.
306. Wolff, B. P.: Ann. Int. Med. 24: 203, 1946.
307. Belezky, W. K. and Unamskaja, R. M.: Ztschr. f. d. ges. Neurol. u. Psychiat. 129: 21, 1930.
308. Ripley, H. S. and Van Sant, H. M.: J. A. M. A. 102: 1917, 1934.
309. Brown, T. and Nunemaker, J. C.: Bull. Johns Hopkins Hosp. 70: 201, 1942.
310. Solomon, H. C., Berk, A., Theiled, M. and Clay, C. L.: Arch. Int. Med. 38: 391, 1926.
311. Bayne-Jones, S.: Internat. Clin. 3: 235, 1031.
312. Hershfield, A. S., Kibler, O. A., Coldy, S., Koenio, M. T., Schmid, O. W. and Saunders, A. M.: J. A. M. A. 92: 772, 1929.
313. Teiteldaum, A. D.: M. Bull. Vet. Admin. 6: 263, 1930.
314. Arkin, A.: Arch. Int. Med. 25: 94, 1920.
315. Gilkey, H. M. and Dennie, C. C.: South. M. J. 32: 1109, 1939.
316. McDermott, E. N.: Quart. J. Med. 21: 433, 1928.
317. Ebedt, B. and Hesse, E.: Arch. f. klin. Chir. 136: 09, 1925.
318. Rosoolsky, I.: Ztschr. f. d. ges. Neurol. u. Psychiat. 90: 188, 1924.
319. Millot-Carpentier, M.: Union méd. du Canada 38: 1069, 1883.
320. Rubino, A. P.: Pub. Health Rep. 42: 2097, 1927.
321. Drgisic, B. and Koludjerski, S.: Arch. f. Kindern. 112: 168, 1937.
322. Morgan, J. A.: M. J. & Rec. 120: 113, 1924.
323. Banker: Quoted by Crohn (325).
324. Yanajido, M.: Chugai Iji-Shimpo, Tokyo 22: 1902.
325. Crohn, B. B.: Arch. Int. Med. 15: 1014, 1915.
326. Ishiwara, K., Ohtawara, T. and Tamura, K.: J. Exper. Med. 25: 45, 1917.
327. Dembo, L. H., Ruh, H. O., Taroo, W. C. and Taylor, G. R.: Am. J. Dis. Child. 29: 182, 1925.
328. Craig, C. F.: The Etiology, Diagnosis and Treatment of Amebiasis, Baltimoro, Williams and Wilkins Co., 1940.
329. Clark, H. C.: Am. J. Trop. Med. 5: 157, 1925.
330. Gerlen, J. N.: Minnesota Med. 17: 18, 1934.

331. Kartulis: Zentralbl. f. Bakt. **37:** 527, 1904.
332. Putney, F. J. and Baker, D. C.: Dis. of Chest **4:** 20, 1938.
333. Stein, A. and Kazan, A.: J. Neuropath. **1:** 32, 1942.
334. Halpert, B. and Ashley, J. D.: Arch. Path. **38:** 112, 1944.
335. Covey, G. W., Rogers, F. L. and Underwood, G. R.: Nebraska M. J. **23:** 123, 1938.
336. Wright, H. W.: Arch. Neurol. & Psychiat. **10:** 226, 1923.
337. Kollmann, A.: Arch. f. Kinderh. **82:** 150, 1927.
338. Langhans, G. L.: Ztschr. f. Kinderh. **39:** 344, 1923.
339. Steber, Dr.: Deutsche. med. Wchnschr. **43:** 1040, 1917.
340. Raudkepp, F.: Folia Neuropath. Eston **6:** 13, 1926.
341. Franconi, G.: Schweiz. med. Wchnschr. **54:** 434, 1924.
342. Hughes, B.: Clin. J. **49:** 368, 1920.
343. Grifi, V.: Policlinico sez. prat. **29:** 292, 1922.
344. Carver, A. E.: Lancet **2:** 1649, 1903.
345. Heim, M.: Deutsche. med. Wchnschr. **26:** 166, 1900.
346. Moore, A. H.: J. A. M. A. **78:** 1197, 1922.
347. Saha, U. N.: Indian M. Gaz. **77:** 734, 1942.
348. Sironi, L.: Pediatria **29:** 397, 1921.
349. Wilkinson, G. T.: Lancet **2:** 979, 1903.
350. Frank, L. L.: Am. J. Digest. Dis. & Nutrition **11:** 195, 1944.
351. Turcan, H.: Presse méd. **30:** 844, 1922.
352. Valerio, A.: Brasil-med. **40:** 309, 1926.
353. Ferrari, G.: Gior. di clin. med. **14:** 745, 1933.
354. Spieth, H.: Virchows Arch. f. path. Anat. **215:** 117, 1914.
355. Lafforgue, M.: Progrès. méd. **25:** 309, 1923.
356. Zau, F. D.: Chinese M. J. **49:** 689, 1935.
357. Abel, E. and Brenas, P.: Arch. de méd. d. enf. **28:** 426, 1925.
358. Flury, F.: Arch. f. exper. Path. u. Pharmakol. **67:** 275, 1912.
359. Girges, R.: J. Trop. Med. **37:** 209, 1934.
360. Rachmanow, A.: Ann. Inst. Pasteur **28:** 181, 1914.
361. Koino, S.: Jap. M. World **2:** 317, 1922.
362. Suyemori, S.: J. M. Assoc. Formosa **239:** 1925.
363. Fülleborn, F.: J. Helminthol. **7:** 15, 1929.
364. Höppli, R.: Virchows Arch. f. path. Anat. **244:** 159, 1923.
365. Yamaguchi, S.: Arch. f. Schiffs- u. Tropen-Hyg. **29:** 589, 1925.
366. Sandwith, F. M.: Lancet **1:** 1362, 1894.
367. Ashford, B. K. and King, W. W.: J. A. M. A. **49:** 471, 640, 642, 1907.
368. Ashford, B. K.: Pract. of Med. in the Tropics **3:** 1848, 1923.
369. Signorelli, A.: Policlinico sez. prat. **18:** 549, 1909.
370. Austregesilo, A. and Gotuzzo, H.: Alienist and Neurol. **30:** 21, 1909.
371. Bondurant, E. D.: J. Nerv. & Ment. Dis. **45:** 228, 1917.
372. Hees, H.: Arch. f. Schiffs- u. Tropen-Hyg. **30:** 141, 1926.
373. Chandler, A. C.: Hookworm Disease, New York, Macmillan Co., 1929.
374. Smillie, W. G. and Spencer, C. R.: J. Educ. Psychol. **17:** 314, 1926.
375. Fülleborn, F.: Arch. f. Schiffs- u. Tropen-Hyg. **30:** 679, 1926.
376. Mya, T.: Indian M. Gaz. **63:** 636, 1928.
377. Manson, P.: Tropical Diseases, Paris, C. Naud, 1904.
378. Rodenwaldt, E.: Arch. f. Schiffs- u. Tropen-Hyg. bieh. **10:** 389, 1908.
379. Anderson, J.: London Sch. Trop. Med. Res. Mem., series **5:** 7, 1924.
380. Külz: Arch. f. Schiffs- u. Tropen-Hyg. **12:** 547, 1908.
381. Chambon, M.: Bull. Soc. path. exot. **26:** 613, 1933.
382. Robles, R.: Bull. Soc. path. exot. **12:** 442, 1919.
383. Mira, M. G.: Riforma med. **50:** 858, 1934.
384. Rodhain, J.: Tr. Roy. Soc. Trop. Med. and Hyg. **30:** 501, 1936.

385. Greenfield, J. G. and Pritchard, B.: Brain 60: 361, 1937.
386. Tsunoda, T. and Shimamura, S.: Wein. med. Wchnschr. 56: 1681, 1906.
387. Edgar, W. H.: J. Roy. Nav. M. Serv. 22: 150, 1936.
388. Vituo, W., Cruz, J. R. and Bautista, L. D.: J. Philippine Islands M. A. 21: 291, 1941.
389. Ferguson, A. R.: Glasgow M. J. 79: 4, 1913.
390. Ferguson, A. R.: J. Roy. Army M. Corps 29: 57, 1917.
391. Müller, H. R. and Stender, A.: Arch. f. Schiffs- u. Tropen-Hyg. 34: 527, 1930.,
392. Day, H. B. and Kenawy, M. R.: Tr. Roy. Soc. Trop. Med. and Hyg. 30: 223, 1936.
393. Bayoumi, M. L.: J. Egyptian M. A. 22: 457, 1939.
394. Espin, J.: Rev. Policlinica Caracas 10: 245, 1941.
395. Thomas, H. M., Jr. and Gage, D. P.: Bull. U. S. Army M. Dept. 4: 197, 1945.
396. Hunt, A. R.: U. S. Nav. M. Bull. 45: 407, 1945.
397. Faust, E. C., Wright, W. H., McMullen, D. B. and Hunter, G. W.: Am. J. Trop. Med. 26: 87, 1946.
398. Yamagawa, K.: Virchows Arch. f. path. Anat. 119: 447, 1890.
399. Taniouchi: Arch. f. Psychiat. 38: 100, 1904.
400. Musgrave, W. E.: Philippine J. Sc. 2: 15, 1907.
401. Kawamura, R. and Yamaguchi, M.: Japan Med. World 1: 1, 1921.
402. Kimura, O : Mitt. ü. allg. Path. u. path. Anat. 1: 375, 1919.

CLINICAL PATTERNS OF UNDIFFERENTIATED AND OTHER ACUTE RESPIRATORY DISEASES IN ARMY RECRUITS[1]

THE COMMISSION ON ACUTE RESPIRATORY DISEASES[2]

From the Respiratory Diseases Commission Laboratory, Regional Hospital, Fort Bragg, N. C.[3]

INTRODUCTION

Over a period of three years the Commission on Acute Respiratory Diseases has been engaged in studies of the common forms of acute respiratory disease as they occur in the Army, and particularly in recruits. Four main lines of approach to the problem have been made: (*1*) observations on the clinical manifestations of the various types of acute respiratory disease; (*2*) studies on the epidemiology of respiratory disease (1, 2); (*3*) attempts to control its incidence by such procedures as the oiling of floors and bedding in barracks (3) and the reduction of crowding in barracks (4); and (*4*) etiological studies, including a) animal inoculations with secretions from the respiratory tract of patients with respiratory disease (5), b) experimental transmission to human volunteers of various respiratory diseases (6, 7, 8), and c) the role of bacteria in the causation of the various types of acute respiratory disease (9, 10). This report deals only with the clinical aspects of the studies.

As a preliminary to an analysis of the clinical data, it was necessary to group cases of acute respiratory disease in some reasonable manner which would allow the classification of clinical and etiological entities. The need for such a classification is obvious. These cases are diagnosed both in civilian and military practice under a variety of labels such as common cold, grippe, influenza, nasopharyngitis, catarrhal fever, tonsillitis, bronchitis, upper respiratory infection, streptococcus sore throat, etc. Such diagnoses are inadequate, in the main, because they are not applied uniformly or by any accepted criteria, and because some of them are etiological diagnoses, usually made without bacteriological or other laboratory confirmation.

[1] This investigation was supported through the Commission on Acute Respiratory Diseases, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Office of the Surgeon General, United States Army, and by grants from the Commonwealth Fund, the W. K. Kellogg Foundation, the John and Mary R. Markle Foundation, and the International Health Division of the Rockefeller Foundation, to the Board for the Investigation and Control of Influenza and Other Epidemic Diseases, for the Commission on Acute Respiratory Diseases.

[2] Members and professional associates of the Commission on Acute Respiratory Diseases were: John H. Dingle, Lt. Col., M.C., A.U.S., Director; Theodore J. Abernethy, Lt. Col., M.C., A.U.S.; George F. Badger, Major, M.C., A.U.S.; Joseph W. Beard, M.D.; Norman L. Cressy, Major, M.C., A.U.S.; A. E. Feller, M.D.; Irving Gordon, M.D.; Alexander D. Langmuir, Major, M.C., A.U.S.; Charles H. Rammelkamp, Jr., M.D.; *Elias Strauss*, Major, M.C., A.U.S.; Hugh Tatlock, Captain, M.C., A.U.S.

[3] Now located in the Department of Preventive Medicine, School of Medicine, Western Reserve University, Cleveland, Ohio.

Three years of study have resulted in a partial description and classification of the clinical syndromes commonly grouped as acute respiratory disease. Various entities have been recognized. The bulk of the remaining cases constitute a clinical entity termed undifferentiated acute respiratory disease (ARD). The great majority of all cases of acute respiratory disease admitted to an army hospital could be classified as follows:

A. *Pneumonia.* Cases with demonstrable pulmonary lesions by roentgenogram were classified as *primary atypical* pneumonia (11) or *bacterial* pneumonia on the basis of clinical history and physical findings, leucocyte counts, and the results of bacteriological study of the sputum. The incidence of primary atypical pneumonia has varied from 5 to 10 per cent of all respiratory admissions (1). Bacterial (mostly pneumococcal) pneumonia has been responsible for less than 2 per cent of all respiratory admissions.

B. *Influenza.* This diagnosis was made on the basis of agglutinin-inhibition tests of acute and convalescent phase sera from all patients. Influenza A and B occurred sporadically in certain periods of the study, but its incidence has been low (12). An epidemic of influenza A occurred in December, 1943 (13).

C. *Exudative tonsillitis* and *pharyngitis.* Approximately 15 per cent of all respiratory admissions had exudate present in the pharynx or on the faucial tonsillar tissue. From the results of throat cultures and serological tests for streptococcal antibodies (antistreptolysin and antifibrinolysin), the cases with exudate were divided into 3 groups: a) *non-streptococcal,* of unknown etiology, constituting half of all cases with exudate; b) *with streptococci* and *with streptococcal antibodies,* —the true streptococcal infections—constituting one-quarter to three-tenths of all cases with exudate; and c) *with streptococci, but without antibodies,* constituting one-fifth to one-quarter of all cases with exudate (9, 14).

D. *Undifferentiated acute respiratory disease* (ARD). The above three categories included no more than from 10 to 25 per cent of all respiratory admissions. The remainder have been grouped together under the noncommittal label of ARD. The diagnosis is one of exclusion, since these cases did not have pneumonia by roentgenogram, influenza by serological test, or exudate in the throat by clinical examination, and, in addition, did not have streptococcal antibodies.

A small but variable number of cases were encountered which belonged in other diagnostic categories. They were excluded from further consideration. These included: immunization reactions (typhoid, tetanus, vaccination), contagious exanthemata, meningococcus infections, and chronic and allergic diseases of the paranasal sinuses and tracheobronchial tree. The criteria used to exclude cases in the latter categories were applied in most, but not in all, instances. It is believed, however, that no serious error has been introduced by the failure to exclude all cases in these categories.

This report will deal with the clinical patterns of the various entities classified above. Clinical descriptions of pneumonia (11) and influenza (13) have been given in other reports and will not be repeated here.

The classification of exudative tonsillitis and pharyngitis into 3 groups and the clinical characteristics and laboratory findings in these groups have been reported (14). These results, based on a relatively small number of cases, were somewhat

at variance with accepted opinions, particularly in regard to the pre-eminent role of β-hemolytic streptococci in the causation of exudative tonsillitis and pharyngitis. Accordingly the studies were repeated and essentially similar results were obtained in a larger series of cases. The epidemiological aspects of this study have been reported (9). In this paper, the combined results of the clinical features of the original and second studies will be described and used as a basis for comparison with ARD.

It is apparent from the foregoing that ARD is the central problem in acute respiratory disease. Epidemiological studies have indicated that it occurs predominantly in recruits. Epidemics of ARD have occurred regularly during the winter months, but not in the summer. Although cases of a similar clinical pattern occurred also in seasoned men, epidemics were not seen (1, 2).

The definition of ARD employed in these studies has been useful to the extent that it has permitted the delineation of the clinical picture and thereby has clarified some of the confusing opinions often stated about this type of common respiratory disease. These results may be summarized at the outset by stating that (*1*) there is no significant variation in the average clinical pattern from one year to another, and in different seasons, (*2*) the syndrome appears to be of nonbacterial, and probable of virus origin, and (*3*) among hospitalized cases, it does not resemble the picture of acute coryza or the "common cold".

For convenience, the four clinical entities with which this report is concerned will be referred to as groups 1, 2, 3, and 4 as follows:

Group 1: undifferentiated acute respiratory disease (ARD),

Group 2: exudative tonsillitis and pharyngitis of unknown etiology (not streptococcal infections or carriers),

Group 3: exudative tonsillitis and pharyngitis due to β-hemolytic streptococci (the true streptococcal infections which produced streptococcal antibodies), and

Group 4: exudative tonsillitis and pharyngitis, with β-hemolytic streptococci, but without streptococcal antibodies.

METHODS

Scope of studies and criteria of selection.—The clinical studies reported here were made on soldiers admitted to the respiratory disease wards at the Regional Station Hospital, Fort Bragg, North Carolina. The studies were limited to members of the Field Artillery Replacement Training Center (FA RTC), an organization devoted to the training of recruits. Ninety per cent of the men had less than 3 months of military experience at the time of admission to the hospital. The great majority were between 18 and 35 years of age. The patients were admitted to the hospital through unit dispensaries, in which the criterion for hospitalization was, in general, an oral temperature of 100° or more.

Four series of clinical studies were selected for analysis. For convenience they will be referred to as the "T", "D", "E", and "O" series (Table 1). The time and duration of each study, the total number of admissions, and the final diagnostic categories to which the cases were assigned, are shown in the table.

The following procedures were carried out on all subjects in each study group, the classification shown in Table 1 was made from the results of these studies:

(*1*) Roentgenograms of the chest were taken routinely on admission, and subsequently as often as indicated by clinical findings.

(*2*) Serum specimens were obtained routinely on admission to the hospital and 3 to 6 weeks later. Tests for antistreptolysin (14) and antifibrinolysin (15) were made on paired sera from all cases in the "T" and "E" series, but only on sera from those cases which harbored β-hemolytic streptococci in the "D" and "O"

TABLE I

Classification of cases of respiratory disease in four series, 1943–1945

	SERIES DESIGNATION AND DATE OF STUDY			
	"T" 4/7–6/10/43	"D" 11/25/43–1/31/44	"E" 3/13–5/21/44	"O" 1/1–31/45
Approx. number admissions to respiratory wards	900	350	860	300
Number of cases studied	116	342	308	286
Basis of selection of cases	exudate	none	exudate and others*	none
Diagnosis:				
ARD—(Group 1)	—	147	149	199
Exudative tonsillitis and pharyngitis:				
non-streptococcal (Group 2)	60	19†	50	47
due to streptococci (Group 3)	28	14	34	5
with strep., no antibody (Group 4)	28		36	4
Influenza A	3	132	0	1
Influenza B	1	3	0	1
Primary atypical pneumonia	90	27	63	17
Bacterial pneumonia	5	0	10	3
Chronic respiratory disease	—	6	6	10
Others, not classified above	—	0	25	4

* = all cases with streptococci in initial cultures; every fifth admission.
— = not determined.
† = also includes cases in Group 4.

series. With each test an increase in titer between acute and convalescent phase sera of 2 or more dilution increments was considered significant, and only patients with such increases in titer in either test were classified as having developed streptococcal antibodies.

In addition all paired sera were tested for influenza A and B antibodies by the agglutinin-inhibition test (13); a diagnosis of influenza was made on the basis of a four-fold or greater increase in titer of convalescent phase sera. None of the subjects had been vaccinated against influenza A or B.

(*3*) Throat cultures were obtained routinely on all patients at the time of admission and β-hemolytic streptococci identified by methods previously described (14). In the "T" and "E" series, 3 consecutive daily cultures were taken and the

patients were considered to harbor β-hemolytic streptococci if any of the 3 cultures contained these organisms. In the "D" and "O" series, a single throat culture was taken.

The methods of selection of cases for study in the various series were as follows:

"T" series. All patients admitted to the hospital from 3 regiments (approximately 9000 men) during a 10-week period in the spring of 1943 were examined; only those with exudate in the throat at the time of admission were included in the study.

"E" series. During a 10-week period in the spring of 1944, all admissions were examined from 3 regiments (9000 men). All patients with exudate were included in the study as well as every fifth consecutive individual without exudate, in order to obtain a representative sample of ARD. The latter group consisted of cases with and without β-hemolytic streptococci, but those who developed streptococcal antibodies were excluded from this category.

TABLE 2

*Numbers and classification of cases used in analyses**

SERIES	GROUP 1 ARD	GROUP 2 EXUDATE—NON-STREP.	GROUP 3 EXUDATE—DUE TO STREP.	GROUP 4 EXUDATE—STREP., NO ANTIBODY
"T"	—	44	23	23
"D"	113	—	—	—
"E"	127	45	31	30
"O"	133	36	—	—
Total.....	373	125	54	53

* See text for group designations.

"D" series. All admissions from 2 battalions (2000 men) were examined during a 2-month period. During December, 1943, 80 per cent of the patients had serological evidence of infection with influenza virus A. During January, 1944, an epidemic of ARD occurred, and an analysis of these cases is included in this report. Since only a single throat culture was made and streptococcal antibodies tested only on those with β-hemolytic streptococci, it is possible that a few cases, included in the ARD group, may have actually harbored these organisms and developed streptococcal antibodies. It is believed that such cases were rare. The number of cases with exudate, both with and without streptococci (Table 1) was too small to permit analysis (Table 2).

"O" series. During the month of January, 1945, at a time when ARD was epidemic, all admissions from a battalion (1000 men) were examined. The cultural and serological procedures in this study were similar to those employed in the "D" series. In the "O" series, therefore, it is also possible that a few cases classified as ARD may have harbored streptococci and developed streptococcal antibodies.

Methods of case study.—All of the cases included in this report were examined within a few hours after admission to the hospital. Approximately 90 per cent of the cases were seen by either of 2 members of the group. A check-form was used for the recording of symptoms and physical signs, and each patient was questioned and examined daily throughout his hospital stay. An attempt was made to record the onset of disease as accurately as possible to the hour and day. The appearance of symptoms was recorded by 12-hour periods during the first 2 days of illness, and daily thereafter. Since some respiratory symptoms of slight degree are common in many healthy persons, an endeavor was made to record symptoms only when they were present in greater than "normal" degree for each individual. In addition, the mode of onset was recorded as "sudden" or "gradual". The onset was defined as "sudden" when a period of less than 24 hours elapsed between the appearance of the first symptom and the time of admission to the hospital. The only additional symptom requiring definition was chest pain. As used in this study, chest pain referred to substernal or subcostal aching or soreness, and not to pleuritic pain.

The presence of abnormal physical signs was recorded by 24-hour periods beginning with the first day of hospitalization. Abnormal physical signs were graded on a scale of severity as mild or moderate (1+), or severe (2+). For example, moderate and "streaky" redness of the mucous membranes of the pharynx and tonsils (1+) was distinguished from diffuse and intense hyperemia (2+). Likewise, discrete patches of exudate on the tonsils or pharynx, varying in size from pinhead to 0.5 cm. in diameter were recorded as 1+, and larger, confluent patches of exudate as 2+.

Each case was classified as mildly ill, or moderately, or severely ill, on the basis of general appearance. "Lymphoid hyperplasia" referred to the appearance of follicles of lymphoid tissue on the pharyngeal mucous membranes; their appearance was recorded as 1+ when the follicles were moderately red, and 2+ when diffusely red and edematous. "Enlarged" cervical lymph nodes were those which were observed to decrease in size during convalescence. The remaining descriptive terms were used in their ordinary clinical sense. In all instances where indicated the final quantitative grading of physical signs and symptoms was revised at the time when the patient was convalescent and ready for discharge from the hospital, and when it was felt that a reasonably "normal" status had been regained.

Throughout all the studies the examiners attempted to achieve and maintain uniformity in the methods of eliciting symptoms and in the grading of abnormal physical signs.

Oral temperatures were recorded twice daily at 8:00 a.m. and 4:00 p.m. Total and differential leucocyte counts were obtained in the great majority of all patients within a day after admission.[4] All patients were kept at bed rest until the temperature was within normal limits for 48 hours. Treatment was, in general, symptomatic and supportive. Various types of nose drops and saline gargles were used freely by most patients. Aspirin and other antipyretic drugs were not

[4] Leucocyte counts were made by the Laboratory Service of the Regional Station Hospital.

administered. Sulfonamides were employed on only a small number of patients; penicillin was not used. Codeine in small doses was administered occasionally for severe headache or cough. Steam inhalations were used in a few instances.

In Table 2 are recorded the numbers of cases, in each diagnostic category in the various series, which were included in the statistical analyses of symptoms and signs. The chief reason for exclusion of cases from analysis was incompleteness of the information on the clinical form. Usually this resulted from inability to date the onset of symptoms; this difficulty arose in approximately 20 per cent of the cases in all groups, and was generally due to the indefinite and insidious nature of the onset of symptoms.

The data were analyzed by several methods:

(1) *Total frequency of* (a) *symptoms* from onset and (b) *physical signs* at any time during the hospital stay.

(2) *Cumulative frequency of onset of symptoms* during the first 5 days of illness. This was analyzed and cumulative totals obtained on a daily basis, by day of illness.

(3) *Prevalence of symptoms* during the first 5 days of illness. This analysis was made by 12-hour periods during the first 48 hours of illness and daily thereafter, except in the "D" series cases where it was made by 24-hour periods throughout the first 5 days of illness.

(4) *Prevalence of physical signs* was tabulated on a daily basis for the first 5 days of illness. Since relatively few patients were observed in the hospital on the first day of illness, the charts depicting the daily prevalence of physical signs begin with the second day of illness.

The total frequency of symptoms and signs is slightly greater in some instances than is indicated in the cumulative frequency of onset charts, due to the termination of the latter observations on the 5th day of illness. Since many patients were not observed later than the fifth day of illness, it was not feasible to continue the analysis beyond that period. Moreover, the additional information to be gained appeared to be negligible.

In all instances, the results by each of the above methods were tabulated separately for each diagnostic group, and the results in similar groups in different series were totaled when it seemed appropriate. The results presented in graphic and tabular form were those which seemed most pertinent to the purposes of this report.

RESULTS

Undifferentiated acute respiratory disease (ARD)—Group 1

Comparison of ARD in 3 series.—The clinical pattern of ARD was remarkably uniform in 3 separate studies. Two of the studies ("D" and "O") were carried out during epidemics of ARD in January, 1944 and January, 1945, respectively; the third study ("E") was carried out during a period of moderately high prevalence of ARD, from March to May, 1944. In Figure 1 is presented the cumulative frequency of onset of representative symptoms. It is evident that feverishness was the outstanding constitutional symptom and that headache and malaise

were less prominent. Nasal symptoms were absent in nearly half of the cases, although nasal obstruction (not shown) was somewhat more frequent than nasal discharge and sneezing. Cough and hoarseness were the most prominent of the symptoms indicative of respiratory tract involvement. The appearance of chest pain lagged considerably behind the appearance of cough. The chief point to be

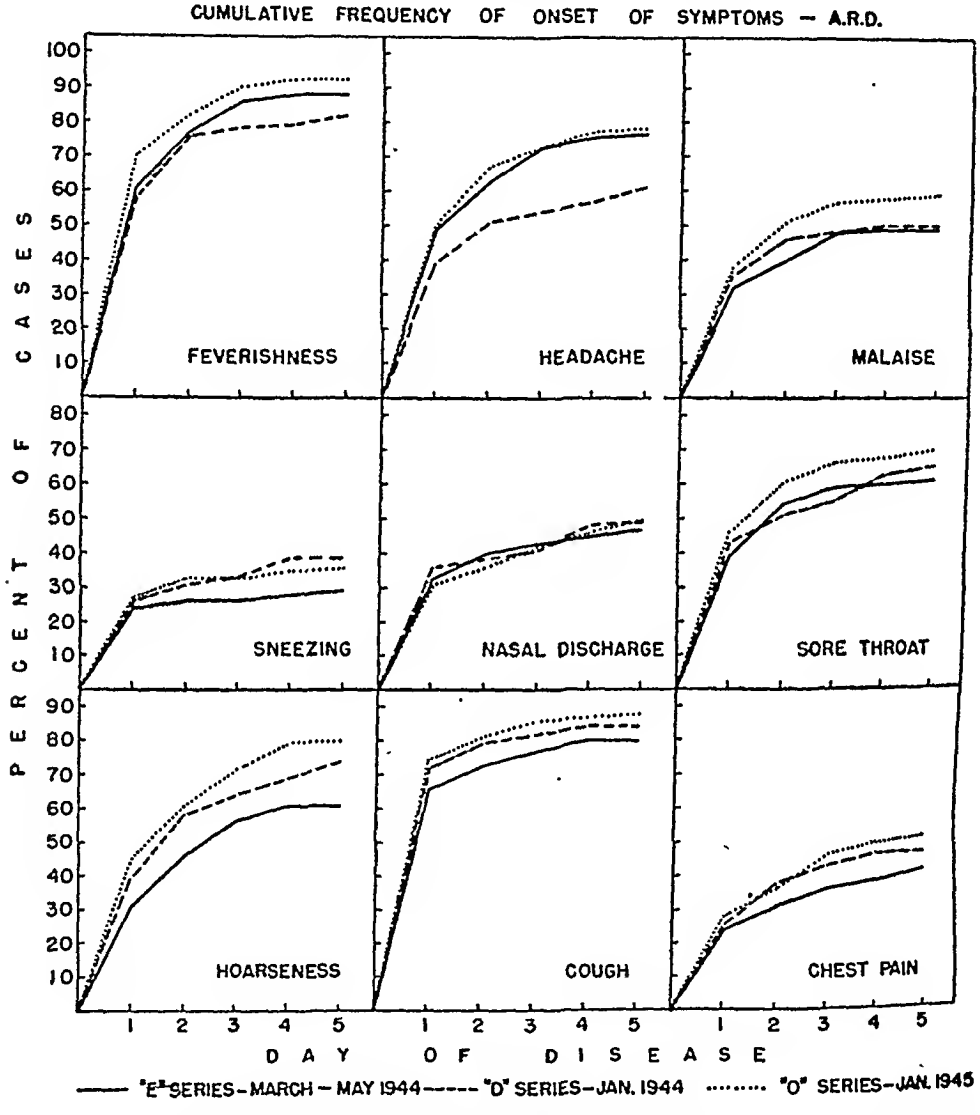


FIG. 1. ONSET OF SPECIFIED SYMPTOMS

Cumulative frequency by day of disease in 3 series of cases of undifferentiated acute respiratory disease (ARD).

emphasized in Figure 1 was the rather close agreement in the total frequency and in the curves of development of symptoms among the 3 individual study groups. The greatest difference noted was in the symptom of hoarseness, where there was a difference of 20 per cent in the total frequency in the "E" series cases as compared with the "O" series. There was possibly also some tendency for the frequency of most symptoms to be greatest in the "O" series, but this was

not marked. This difference was probably due to slight variations in the technique of recording symptoms from one study to another.

In Figure 2 is depicted the daily prevalence of the principal symptoms in the series of ARD cases. It can be seen that the constitutional symptoms (feverishness, headache, malaise) had their greatest frequency in the early stages of illness

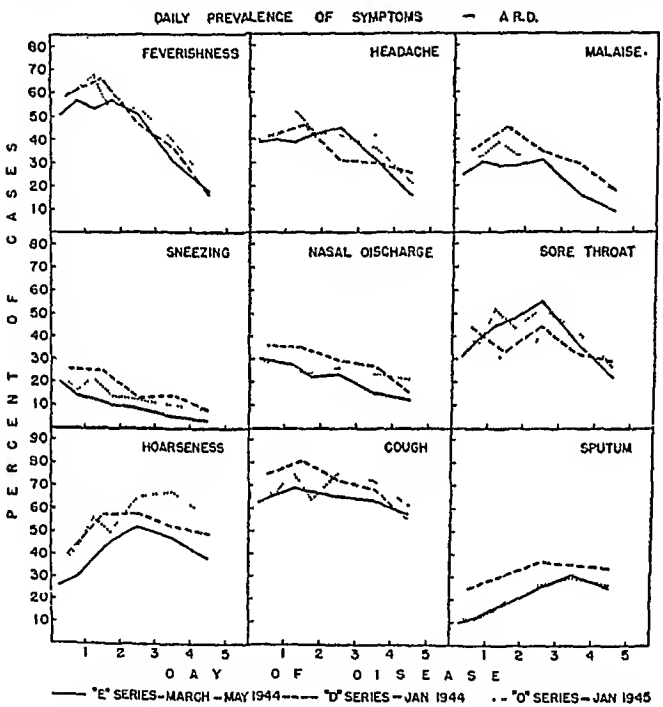


FIG. 2. PREVALENCE OF SPECIFIED SYMPTOMS BY DAY OF DISEASE IN 3 SERIES OF CASES OF UNDIFFERENTIATED ACUTE RESPIRATORY DISEASE (ARD)

In the "E" and "O" series, rates are recorded by 12-hour periods for the first 2 days and daily thereafter. In the "D" series the rates are recorded on a daily basis throughout.

and tended to disappear by the fifth day. On the contrary, localized symptoms of involvement of the respiratory tract (sore throat, hoarseness, cough and sputum) persisted longer and tended to reach their maximum frequency later in the illness. The frequency and daily prevalence of symptoms was quite similar in the 3 series. The data shown in Figures 1 and 2 indicate that the clinical pattern of ARD was similar during the 3 studies and allow the 3 series to be totaled for comparison with other diagnostic groups of cases.

Comparison of ARD with exudative tonsillitis of streptococcal and unknown etiology.—In Figures 3, 4, 5 and 6, a comparison was made of the symptoms and physical signs in ARD and other clinical entities. For these figures the total results of comparable groups in each series were added together (Table 2). That

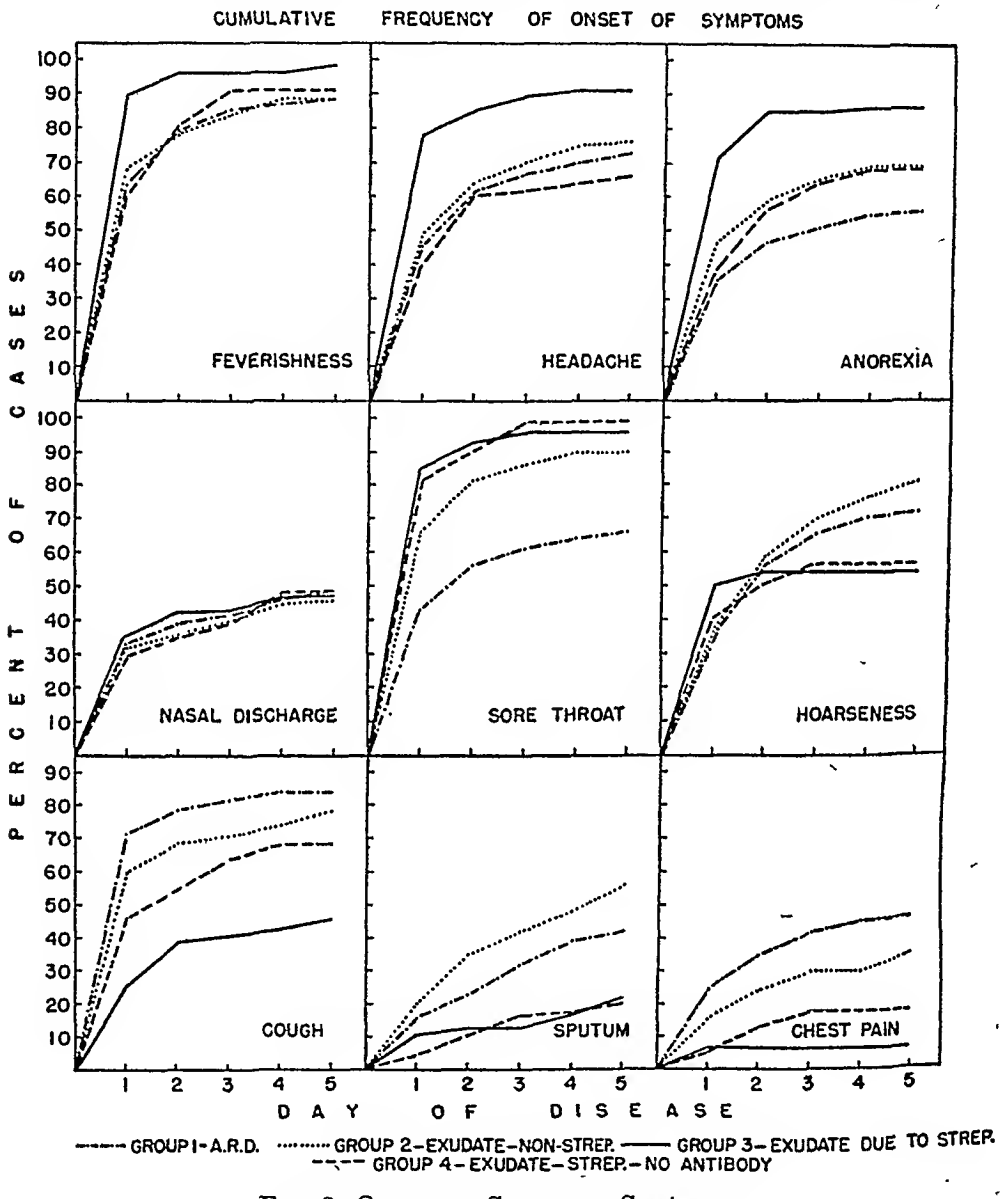


FIG. 3: ONSET OF SPECIFIED SYMPTOMS
Cumulative frequency by day of disease in 4 groups of cases

this addition is valid was shown above in the case of ARD. For the sake of brevity, similar comparisons of the individual series are not presented for the other clinical categories, but the results in these groups also indicated close similarity. In the following charts, then, the frequency and prevalence of symptoms and physical signs are compared for all cases of: a) ARD (Group 1); b) exudative tonsillitis and pharyngitis of non-streptococcal (unknown) etiology (Group 2);

c) exudative tonsillitis and pharyngitis due to β-hemolytic streptococci and with streptococcal antibodies (Group 3); and d) exudative tonsillitis and pharyngitis with β-hemolytic streptococci present in culture, but without streptococcal antibodies (Group 4).

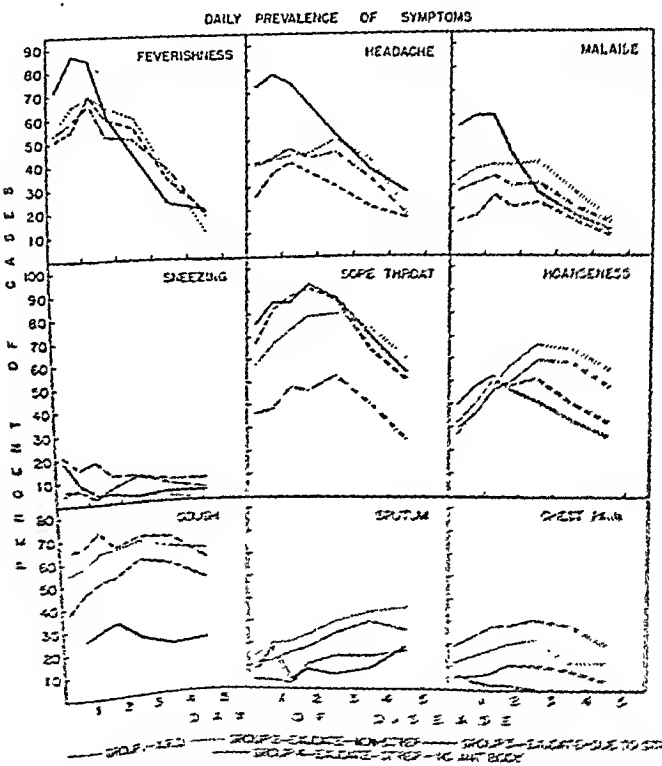


FIG. 4. PREVALENCE OF SELECTED SYMPTOMS BY DAY OF DISEASE IN 4 GROUPS OF CASES

Because of a difference in the frequency with which symptoms were recorded, cases in the "D" series are omitted from Group 1 [illegible]

ARD [illegible] clinical [illegible] 3, in some respects [illegible] of various symptoms [illegible] but differed from Group 2. The frequency and rapidity of development of headache, malaise and stiffness [illegible] the same for all groups,

except Group 3. The frequency of nasal discharge was almost identical for all groups; sore throat was decidedly less common in ARD than in the categories

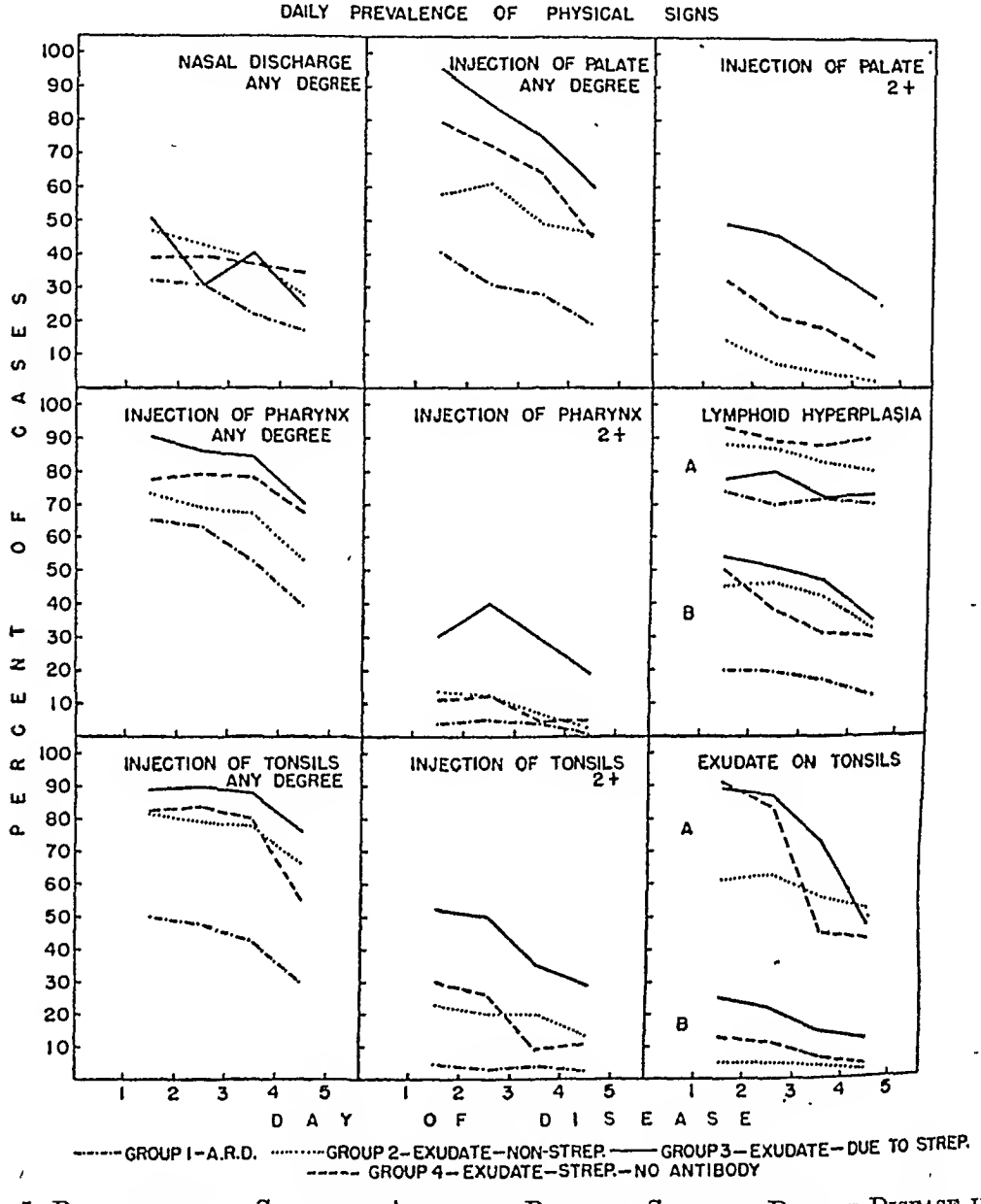


FIG. 5. PREVALENCE OF SPECIFIED ABNORMAL PHYSICAL SIGNS BY DAY OF DISEASE IN 4 GROUPS OF CASES

For the significance of 2+, see text. In the graph labeled "lymphoid hyperplasia" the upper set of curves (A) indicates the prevalence of moderately red lymphoid follicles on the pharyngeal wall, and the lower set of curves (B) indicates the prevalence of diffusely red and edematous follicles. Under "exudate on tonsils", the upper set of curves (A) indicates the presence of exudate of any extent, and the lower set (B) indicates the prevalence of confluent exudate.

where exudate was present. However, symptoms suggesting involvement of the lower respiratory tract were more common in ARD and non-streptococcal exuda-

tive tonsillitis and pharyngitis than in those cases of exudative tonsillitis and pharyngitis with streptococci (Groups 3 and 4). The daily prevalence of symp-

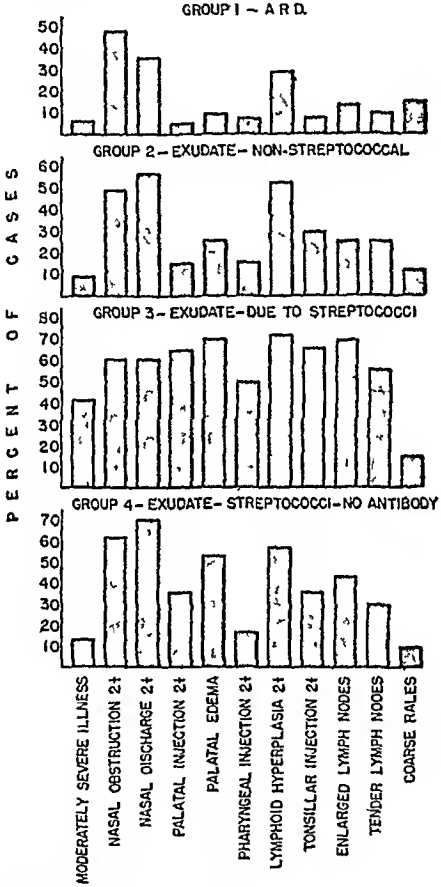


FIG. 6. TOTAL FREQUENCY OF VARIOUS ABNORMAL PHYSICAL FINDINGS AT ANY TIME DURING HOSPITAL COURSE IN 4 GROUPS OF CASES

For the significance of 2+, see text

toms in the various groups (Figure 4) revealed relationships similar to those seen in Figure 3. Noteworthy was the low frequency of symptoms referrable to nasal involvement. Although sneezing was slightly more common in ARD than in the other groups, its total frequency was only 35 per cent.

In Figure 5 is depicted the daily prevalence of some of the abnormal physica signs found in the groups under consideration. It is apparent that in every in stance the various abnormal findings were less prevalent in ARD than in any o the other groups. Even evidence of nasal involvement was less common in thi group than in the other groups. In all instances, severe degrees of involvement, such as diffuse redness of the palate, pharynx, and tonsils were found in less than 10 per cent of the cases of ARD. This contrast between ARD and other cate-

TABLE 3

Duration of fever of 100°F. (oral) or more and average maximum temperature

HOSPITAL DAYS OF FEVER	GROUP 1 ARD	GROUP 2 EXUDATE—NON-STREP.	GROUP 3 EXUDATE—DUE TO STREP.	GROUP 4 EXUDATE—STREP., NO ANTIBODY
	per cent	*per cent*	*per cent*	*per cent*
0	19	11	0	17
1	29	23	23	28
2	28	29	34	21
3	13	21	21	17
4	7	12	4	9
5 or more	4	5	19	7
Average maximum temperature.....	101.1°	101.7°	102.5°	101.5°

TABLE 4

Per cent of cases with low, normal, and elevated total leucocyte counts and average per cent of polymorphonuclear leucocytes during first 4 days of illness

	TOTAL LEUCOCYTES PER CU. MM.			AVERAGE PER CENT POLYMORPHONUCLEAR LEUCOCYTES
	6,000	6,000–9,999	10,000 or more	
	per cent	*per cent*	*per cent*	
Group 1—ARD.....	12	61	28	66
Group 2—Exudate—non-strep.....	10	55	36	67
Group 3—Exudate—due to strep.....	2	16	82	79
Group 4—Exudate—strep., no antibody.....	13	48	40	67

gories is brought out also in Figure 6 which depicts the total frequency of various abnormal physical signs. ARD is indeed a disease without physical findings.

ARD was also a disease of short febrile course (Table 3). Nearly 50 per cent of the cases had less than 2 days of fever of 100° F or more (oral) after admission to the hospital; 40 per cent had from 2 to 3 days of fever, and only 10 per cent had more than 3 days of fever of this magnitude. The duration of fever in the hospital was more prolonged in all other groups. The average maximum temperature in the hospital in the ARD group was 101.1° F.

The total leucocyte count in ARD was usually within normal limits. The average total leucocyte count in 246 cases was 8354 per cu. mm. (Figure 7). Total counts of 10,000 or more were found in 28 per cent of the cases (Table 4). The differential formula in ARD was essentially normal; the average per cent of polymorphonuclear leucocytes was 66 per cent.

In summary, ARD exhibited a uniform average pattern which was maintained in three separate studies in January, 1944, March–May, 1944 and January, 1945. It was a disease of short course with fever of 100° F or more for less than 3 days in the great majority of cases and an average maximum temperature of 101.1° F.

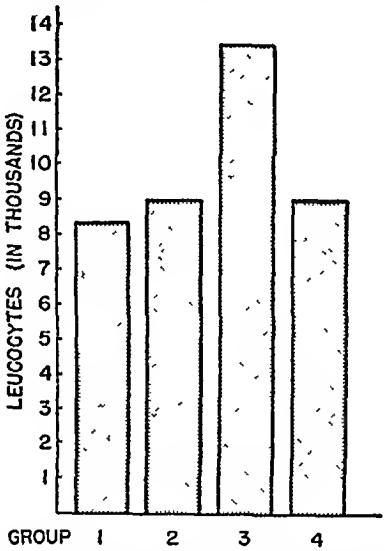


FIG. 7. AVERAGE TOTAL LEUCOCYTE COUNT IN VARIOUS GROUPS OF CASES

Group 1—ARD; Group 2—exudate, non-streptococcal; Group 3—exudate, due to streptococci; Group 4—exudate with streptococci on culture, but no antibody.

Only rarely (5 per cent) did the patients appear moderately or severely ill (Figure 6). The onset was gradual (Figure 8). Ninety per cent of patients complained of feverishness, and 75 per cent of chilliness and headache. Malaise and anorexia and symptoms of nasal involvement were noted by only half of the patients. Sore throat was a common complaint, but was less frequent and less severe than in patients with exudate in the throat. Symptoms of involvement of the lower respiratory tract were prominent—more so, in general, in cases of ARD than in any of the other groups. In keeping with the short febrile course, the constitutional symptoms disappeared quickly. However, the local symptoms of involvement of the respiratory tract, particularly cough and hoarseness

were more persistent and frequently remained even when the patient left the hospital. Physical signs were notably few and rarely of intense or severe degree. The most frequent were signs of nasal involvement (obstruction and discharge), although these were present in less than half of the cases. Despite the prominence of cough, sputum, and subcostal and substernal pain, râles were detected in not more than 15 per cent of patients.

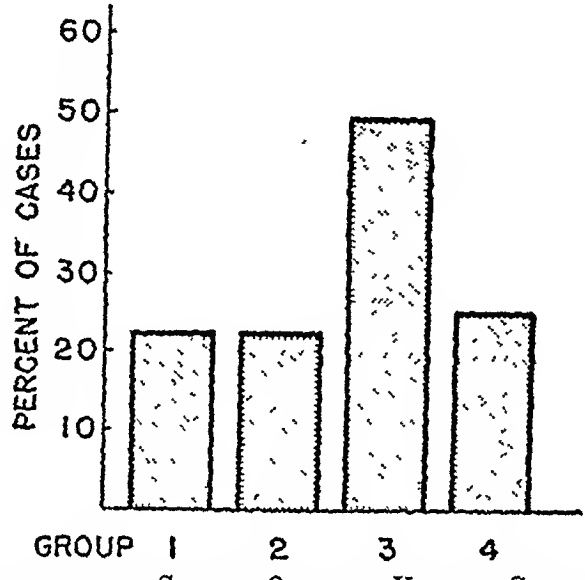


FIG. 8. FREQUENCY OF SUDDEN ONSET IN VARIOUS GROUPS OF CASES

For the definition of "sudden onset", see text. Groups 1, 2, 3, and 4 are the same as in Figure 7.

Exudative tonsillitis and pharyngitis of non-streptococcal (unknown) etiology—Group 2

The clinical pattern of this condition has already been described (9, 14, 16). In the present report this description is amplified by the inclusion along with the original data ("T" series) of two additional series of cases ("E" and "O"). The present description is based on an analysis of 125 cases (Table 2).

The clinical features of non-streptococcal exudative tonsillitis and pharyngitis (Group 2) are presented in Figures 3–8. In general, this group of cases was intermediate between ARD (Group 1) and streptococcal exudative pharyngitis and tonsillitis (Group 3); in some of its characteristics it resembled both of these other groups. Like ARD, it was a mild disease of short duration. Only 10 per cent of the patients appeared more than mildly ill while in the hospital (Figure 6). Constitutional symptoms were more frequent in Group 2 than in ARD (Group 1), but less frequent than in Group 3 (Figure 3). This relationship between the 3 groups was also true of sore throat. In contrast, symptoms of involvement of the lower respiratory tract were as frequent in Group 2 as in ARD. Nasal symptoms, in this group, as in the other categories, were not prominent features of the disease. There was a definite tendency for the maximum prevalence of symptoms to occur later in the course of illness in Group 1 and 2 than in

Groups 3 or 4 (Figure 4). This was especially noted in such localizing symptoms as hoarseness, soreness of the throat, cough, sputum, and chest pain, all of which reached their maximum prevalence on the third day after onset or later, at a time when the constitutional symptoms were beginning to decrease in frequency.

Non-streptococcal exudative tonsillitis and pharyngitis was also in an intermediate position between ARD and streptococcal tonsillitis and pharyngitis in regard to the abnormal physical signs present. The chief abnormal findings in non-streptococcal exudative tonsillitis and pharyngitis were in the appearance of the throat. This group of cases, by definition, was characterized by the finding of exudate in the throat. The exudate was usually small in amount and the individual spots were often pinhead in size and rarely confluent (Figure 5). Frequently the patches of exudate were pearly-gray in color and surmounted swollen lymphoid follicles. In contrast to ARD, the mucous membranes of the palate, pharynx, and tonsils were injected in the majority of cases; like ARD, however, this injection was not often of severe degree and was "streaky" rather than diffuse. Prominent lymphoid follicles were seen on the pharyngeal wall in almost all cases and in nearly half of the cases these follicles were red and swollen. Often they had the appearance of bands along the posterior tonsillar pillars. The intermediate position of non-streptococcal tonsillitis and pharyngitis with regard to the frequency of physical signs is also illustrated in Figure 6. It will be noted that enlarged and tender lymph nodes in the anterior triangles of the neck were present in 25 per cent of cases. This is in sharp contrast with the prominence of these findings in streptococcal tonsillitis and pharyngitis. It is also of interest that despite the frequency of cough, sputum, and chest pain, less than 15 per cent of cases had râles in the chest.

The duration of fever in Group 2 cases was slightly longer than in Group 1 cases (Table 3). Fifty per cent of the cases has fever lasting 2 or 3 days; in 17 per cent fever was prolonged for more than 3 days; and 34 per cent had less than 2 febrile days in the hospital. The average maximum temperature was 101.7° F.

The average total leucocyte count in 184 cases (during the first 4 days of illness) was 9024 per cu. mm. (Figure 7). A number of cases had definite leucocytosis; in 36 per cent of the cases the total count was 10,000 or more (Table 4). The differential formula was normal; the average per cent of polymorphonuclear leucocytes was 67 per cent.

The non-streptococcal type of exudate occurred more frequently in patients without faucial tonsils or with only tonsillar "tags" than did exudate due to streptococcal infection. Both streptococcal and non-streptococcal infections, however, were most frequent in patients who had not had a tonsillectomy performed. A few cases of Vincent's tonsillitis were included, by definition, in Group 2. These cases were clinically distinctive and easily separated from the other cases of non-streptococcal exudative tonsillitis.

Exudative tonsillitis and pharyngitis due to β-hemolytic streptococci—Group 3

The clinical picture of this entity has been described in a previous report (14). The original study ("T" series) was repeated in an identical manner in the "E"

series, and with confirmatory results. The totals of the two series are here combined and are presented in Figures 3–8 for comparison with the other groups of cases described above.

Exudative tonsillitis and pharyngitis due to β-hemolytic streptococci (Group 3) had a distinctive clinical pattern which, on the whole, was readily distinguished from non-streptococcal exudative tonsillitis and pharyngitis (Group 2). In some individual cases, clinical differentiation was difficult (16), but in the majority the distinction could be made. The pattern of streptococcal infection was quite distinct from that of ARD, not only in regard to the presence of exudate, but also with regard to symptoms and physical findings.

Unlike the other clinical groups described, the onset of illness in streptococcal tonsillitis and pharyngitis was often sudden; half of the cases reached the hospital within 24 hours after the first symptom (Figure 8). Constitutional symptoms developed rapidly and reached greater frequency than in the other entities described (Figure 3). Sore throat was almost always present, but hoarseness, cough, sputum and chest pain were much less common. Nasal symptoms were not prominent. Most of the symptoms had their greatest prevalence early in the illness and decreased rapidly thereafter (Figure 4).

In the main, this group of cases was characterized by distinctive physical findings (Figure 5). Not only was some degree of redness of the mucous membranes of the palate, pharynx, and faucial tonsils present almost universally, but severe degrees of inflammation were also commonly seen. The mucous membranes, and particularly the uvula, were often edematous. The exudate was usually larger in amount, yellow in color, and confluent in extent. Two-thirds of the cases had enlarged cervical lymph nodes and most of them also complained of soreness in these nodes. Nearly half of the patients appeared to be more than mildly ill on admission to the hospital. The contrast between the frequency of physical signs in this group and in Groups 1 and 2 is illustrated in Figure 6.

These patients had a somewhat longer duration of fever in the hospital than patients in the other diagnostic groups (Table 3). This may, in part, be explained by their admission to the hospital earlier in the course of illness. However, this entity, like the others, was essentially one of short duration; 55 per cent of the cases had fever for only 2 to 3 days. The maximum temperature in these cases was higher than in the other groups, averaging 102.5° F.

Exudative tonsillitis and pharyngitis due to β-hemolytic streptococci was characterized by definite leucocytosis. The average total leucocyte count in 50 cases during the first 4 days of illness was 13,427 per cu. mm. (Figure 7). More than 80 per cent of the cases had total counts of 10,000 or more (Table 4). This elevation was dependent on an increase in the polymorphonuclear leucocytes, which averaged 79 per cent in the differential counts.

Exduative tonsillitis and pharyngitis with streptococci but without antibodies—Group 4

It has been pointed out that in the absence of the demonstration of streptococcal antibodies, the presence of streptococci in culture does not warrant a

diagnosis of streptococcal infection (9, 14). One of the points of evidence for this statement was the fact that the clinical pattern of cases without antibodies differed from that of cases with antibodies and more nearly resembled the pattern of cases with non-streptococcal exudate.

The totals of the "T" and "E" series were combined for Group 4 cases. In general, in frequency, time of onset (Figure 3) and daily prevalence (Figure 4), the symptoms of Group 4 cases were intermediate between those of Groups 2 and 3. The same was true of the physical signs in the throat. Clinically, however, it was usually impossible to distinguish between non-streptococcal exudative tonsillitis and pharyngitis, and cases with exudate from which streptococci were recovered by culture but antibodies did not develop. With respect to the duration of fever (Table 3), average height of the leucocyte count (Figure 7), and per cent of cases with elevation of the leucocyte count to 10,000 or more (Table 4), these 2 groups were similar.

The definition of an antibody response employed in these studies (rise in titer of 2 or more dilution increments) is somewhat arbitrary. Without doubt, some true streptococcal infections have a smaller antibody response (17). In the present study, rises in titer of antistreptolysin of 1 dilution increment were one and a half times as frequent in Group 4 (exudate with streptococci) as in Group 2 (exudate without streptococci). Therefore, some cases which were true streptococcal infections were undoubtedly included in Group 4. These cases were *probably responsible for raising the general levels of the prevalence* of symptoms and physical signs in Group 4 nearer to the levels of the true streptococcal cases (Group 3).

Effect of streptococci on the pattern of ARD.—Approximately one-third of the ARD cases in the "E" series had streptococci on one or more of 3 cultures and two-thirds had no streptococci in any of three cultures. All cases had less than a 2-tube rise in antistreptolysin titer between acute and convalescent phase serum. These two groups were analyzed separately by all of the methods described above. There was very close agreement in all respects between those cases of ARD with streptococci and those without. Thus, it appears that in the absence of exudate, streptococci in the throat which do not stimulate an antibody response do not influence the clinical pattern of illness and cannot be held responsible for the disease.

On the contrary, there were also a small number of patients who had no exudate in the throat, but harbored streptococci and developed antibodies. These patients resembled Group 3 cases in most respects, except for the presence of exudate. In particular, some of these patients had elevated leucocyte counts, diffuse injection of the throat, and enlarged and tender cervical lymph nodes. These clinical features were thus different from the usual findings in ARD. There were too few cases in this category to permit analysis of the data.

DISCUSSION

The syndrome of undifferentiated acute respiratory disease (ARD) is well known, but largely ignored. It occurs in epidemic form under the conditions of

military life, particularly in recruits. In the experience at Fort Bragg during the past 3 years, it has been responsible, during the winter months, for 75 per cent of all admissions to the hospital. Under the terms "febrile catarrh" (18), and "catarrhal fever" (19), the occurrence of a similar epidemic syndrome has been recorded. Its occurrence in civilian life can be assumed from the frequency of such diagnoses as "febrile cold", "grippe", "flu" and the like.

The interest of most investigators of respiratory disease has been directed toward this condition largely insofar as it is confused with infections due to the influenza viruses. While it was earlier believed that the "febrile catarrhs" could be differentiated clinically from influenza (18, 20), recently, and especially since the recognition of influenza B, it has become apparent that the distinction between epidemics of acute febrile illnesses due to influenza and of unknown cause cannot be made readily in many instances (21, 22). The experience in this laboratory has been entirely confirmatory of this point of view (13).

The present study yields no evidence that ARD is related to the "common cold". It is not primarily a coryzal syndrome (23). Nasal symptoms are scarcely more prominent than in such a well-defined etiological entity as streptococcal tonsillitis. It may be argued that the condition described is the result of febrile complications following acute coryza. This is unlikely because the majority of all patients gave no history suggesting coryza or other respiratory symptoms in the week preceding hospital admission. Furthermore, there was no evidence from clinical examination or the results of bacterial cultures that any significant proportion of these patients suffered from localized bacterial infections in the respiratory tract or its appendages.

An epidemiological and clinical relationship between the occurrence of epidemics of primary atypical pneumonia and minor respiratory illness has been pointed out (1, 24, 25, 26, 27). Also under experimental conditions, the inoculation of volunteers with primary atypical pneumonia filtrates resulted in both atypical pneumonia and minor respiratory illness (7). It is entirely reasonable to expect, therefore, that some cases of ARD are due to the agent or agents of primary atypical pnemuonia. In the absence of a specific diagnostic test for primary atypical pneumonia, it is impossible to confirm this supposition.

Extensive bacteriological studies have yielded no evidence incriminating any of the common bacteria as etiological agents of this disease. The throat flora of such patients is the same as that of well soldiers (10). It seems most probable that this syndrome is of non-bacterial origin and is due to one or more viruses. Nasopharyngeal secretions from cases of ARD have been inoculated in a variety of laboratory animals without evidence of the transmission of an infectious agent (28). However, by means of experiments in human volunteers, it has been demonstrated that at least two filterable agents are responsible for minor respiratory illness (8).

The uniformity of the epidemiological pattern of ARD suggested its causation by one agent. The average clinical picture was also uniform in two winter months (January, 1944; January, 1945) and in the spring of 1944. Whether this uniformity is due in part to the selection of only febrile (hospital) cases for study

is not known. Such uniformity might be explained on the basis that (*1*) the syndrome is due to a single agent, (*2*) that it is due to more than one agent, but each produces the same clinical picture, or (*3*) that it is due to more than one agent, each producing a different clinical pattern, but that the proportion of illnesses due to each agent remained constant during the 3 studies.

Exudative tonsillitis and pharyngitis has been a minor part of the total respiratory disease problem at this Post. The present studies confirm and extend previous reports from this laboratory indicating that about half of the cases of exudative tonsillitis and pharyngitis are not related to hemolytic streptococci, and that in those cases which do harbor streptococci, many are not true streptococcal infections. The clinical features of true streptococcal infections of the throat, as reported in these studies, are in general agreement with the findings of others (29, 30). The majority of these cases can be recognized clinically; a certain number cannot. These exceptions are numerous enough, however, to make unsatisfactory routine clinical diagnoses, unsupported by bacteriological and serological study.

Non-streptococcal exudative tonsillitis and pharyngitis also presents a fairly characteristic appearance; so much so, that, in general, the clinical prediction that a given case of exudative tonsillitis will not yield hemolytic streptococci on culture can be made with a fair degree of accuracy. The clinical picture of this syndrome is not far removed from that of ARD when exception is made of such signs and symptoms as are directly related to the local inflammation in the pharynx. Similar findings have recently been reported by Keith and Carpenter (30).

The etiology of these cases is also unknown. There is no evidence that any appreciable number of them are due to bacteria. Although a few instances of Vincent's angina have been included with the cases of non-streptococcal exudative tonsillitis and pharyngitis, such cases are readily separated on clinical grounds; moreover, they constituted less than 8 per cent of all non-streptococcal exudative tonsillitis and pharyngitis cases.

Non-streptococcal exudative tonsillitis and pharyngitis has occurred in rather close relationship to ARD. Others have previously noted that during epidemics of acute respiratory disease of unknown cause, a variable proportion of the cases had exudate in the throat, from which hemolytic streptococci could not be recovered (18, 20, 30). This fact, together with similarity of the clinical picture of ARD and non-streptococcal exudative tonsillitis and pharyngitis, suggests that the latter may be merely a variety of ARD. Since streptococcal infections are not common and ARD constitutes more than 75 per cent of all respiratory admissions, such a supposition would explain why the non-streptococcal type is the prevailing form of exudative tonsillitis and pharyngitis among recruits at this Post. Conversely, among groups of soldiers in which hemolytic streptococci are more prevalent and ARD less so, the ratio between streptococcal and non-streptococcal exudative tonsillitis and pharyngitis would be altered proportionately.

18. Stuart-Harris, C. H.; Andrewes, C. H.; and Smith, W., with Chalmers, D. K. M.; Cowen, E. G. H.; and Hughes, D. L. A study of epidemic influenza: with special reference to the 1936–37 epidemic. Medical Research Council, Spec. Rep. Series No. 228, His Majesty's Stationery Office, London, 1938.
19. Personnel of Naval Laboratory Research Unit #1. The diagnosis of influenza and acute catarrhal fever. U. S. Naval Medical Bull., 42: 27–33, 1944.
20. Francis, T., Jr. Epidemic influenza: studies in clinical epidemiology. Ann. Int. Med., 13: 915–922 (Dec.) 1939.
21. Stuart-Harris, C. H. Influenza epidemics and the influenza viruses. Brit. M. J., 1: 209 (Feb. 17) 1945.
22. Hare, R.; Hamilton, J., and Feasby, W. R. Influenza and similar respiratory infections in a military camp over a period of three years. Canad. J. Pub. Health, 34: 453–464 (Oct.) 1943.
23. Van Volkenburgh, V. A. and Frost, W. H. Acute minor respiratory diseases prevailing in a group of families residing in Baltimore, Maryland, 1928–1930; prevalence, distribution and clinical description of observed cases. Am. J. Hyg., 17: 122–153 (Jan.) 1933.
24. Reimann, H. A., and Havens, W. P. An epidemic disease of the respiratory tract. Arch. Int. Med., 65: 138–150 (Jan.) 1940.
25. Iverson, Herman A. An epidemic of acute respiratory disease associated with atypical pneumonia. Bull. Johns Hopkins Hosp., 72: 89–100 (Feb.) 1943.
26. Breslow, Lester. Epidemic of acute respiratory disease associated with atypical pneumonia. J. Clin. Invest., 24: 775–779 (Nov.) 1945.
27. Favour, C. B. Infections associated with an epidemic of primary interstitial pneumonia. New England J. Med., 230: 537–542 (May 4) 1944.
28. Commission on Acute Respiratory Diseases. Unpublished observations.
29. Felty, A. R., and Hodges, A. B. A clinical study of acute streptococcus infection of the pharyngeal lymphoid tissue (acute follicular tonsillitis). Bull. Johns Hopkins Hosp., 34: 330–335, 1923.
30. Keith, J. D., and Carpenter, J. The diagnosis of haemolytic streptococcal infection in acute nasopharyngitis. Canad. J. Pub. Health, 37: 127–139, 1946.

BACTERIOLOGICAL FINDINGS IN UNDIFFERENTIATED AND OTHER ACUTE RESPIRATORY DISEASES[1]

THE COMMISSION ON ACUTE RESPIRATORY DISEASES[2]

From the Respiratory Diseases Commission Laboratory, Regional Hospital, Fort Bragg, N. C.[3]

The relationship of the aerobic bacterial flora of the respiratory tract to minor acute respiratory illness has been a matter of study and speculation for many years. Prior to 1920 some investigations (see ref. 1 for a summary of early reports) were "open to criticism largely because of their failure to include adequate control studies of the normal flora of the nose and throat" (2). Careful work since that time (2–28) has led to contradictory or inconsistent results. In these studies, a variety of bacteriological techniques, methods of study and control, and ways of summarizing the data have been used. The necessity for such diverse approaches to the problem reflects the difficulties involved in attempting to obtain unequivocal results.

By one worker or another, most of the common inhabitants of normal human throats have been assigned the role of inciting a "cold" or of invading secondarily the tissues of the respiratory tract soon after the primary infection has been established. Even though it has been recognized for some time (29–31, 13,17) that many colds are incited by a filtrable agent, a viral etiology has not been accepted for all minor respiratory illnesses. For this reason such recent studies as that of Straker et al (27), and that to be described in the present report have been made to accumulate more evidence in the matter.

The purpose of this paper is to bring together from several studies made by the Commission on Acute Respiratory Diseases, data bearing on the relationship of the bacterial flora of the pharynx to minor respiratory diseases. Because of the variety of data, a brief description of their sources will introduce the report.

GENERAL DESCRIPTION OF STUDIES

During the course of these studies, three classes of individuals were observed clinically and bacteriologically: *1)* platoons of soldiers on duty, *2)* human volun-

[1] This investigation was supported through the Commission on Acute Respiratory Diseases, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Office of the Surgeon General, United States Army, and by grants from the Commonwealth Fund, the W. K. Kellogg Foundation, the John and Mary R. Markle Foundation, and the International Health Division of the Rockefeller Foundation, to the Board for the Investigation and Control of Influenza and Other Epidemic Diseases, for the Commission on Acute Respiratory Diseases.

[2] Members and professional associates of the Commission on Acute Respiratory Diseases were: John H. Dingle, Lt. Col., M.C., A.U.S., Director; Theodore J. Abernethy, Lt. Col., M.C., A.U.S.; George F. Badger, Major, M.C., A.U.S.; Joseph W. Beard, M.D.; Norman L. Cressy, Major, M.C., A.U.S.; A. E. Feller, M.D.; Irving Gordon, M.D.; Alexander D. Langmuir, Major, M.C., A.U.S.; Charles H. Rammelkamp, Jr., M.D.; Elias Strauss, Major, M.C., A.U.S.; Hugh Tatlock, Captain, M.C., A.U.S.

[3] Now located in the Department of Preventive Medicine, School of Reserve University, Cleveland, 6, Ohio.

furlough was missed. With some of the platoons the first observation consisted of culturing and interviewing, with others, merely of culturing. At each observation after the first, however, both culturing and interviewing were done.

The platoons consisted of men of all degrees of intelligence and cooperation. Because of this, the reliance which can be placed upon their answers is not very great, especially with regard to the more detailed questions. The information elicited was probably most accurately summarized by their responses to the question, "Have you had a cold during the past week?". Therefore, only this item was tabulated with respect to bacteriology. For the most part, the "colds" as tabulated were those of such minor severity as not to warrant hospitalization and have been termed "minor respiratory illness". They refer to a degree of illness which is quite different from that found in the group of hospitalized patients.

2. Volunteers.—The first throat cultures were obtained on May 18 from 35 men in isolation. By May 25 the number in isolation had reached 40. With two exceptions the 40 men remained in isolation until July 4. The first experiment ended on July 6. Between July 4 and July 10 many of the original group of subjects left the study and were replaced by new subjects. The second experiment is considered to have begun on July 8, and during its course observations were made of 43 men, 16 of whom had been in the previous experiment. The full complement of volunteers was not obtained until July 26, but with one exception all men were in isolation and cultured on July 16. No men were dropped from observation until the experiment ended on August 29. Results of cultures are included for each man during the period he was in isolation.

3. Hospitalized Patients.—The method of selecting hospitalized patients for study has been described in detail elsewhere (33). During certain periods of the studies all admissions from selected organizations were included. At other times certain clinical criteria determined the selection of the study group. Patients hospitalized from the platoon groups, described above, were always included; the subjects studied from other organizations were also, for the most part, recently inducted into the army. The population groups being studied usually experienced epidemics of ARD (34) while under observation.

A further selection from the cases studied was made for purposes of the present report. In order to compare the bacteriological results of various diagnostic classes, it was considered to be necessary that:

a) In so far as was possible to determine, a patient should present the characteristics of only one diagnostic class. If he had multiple diagnoses he was excluded from consideration.

b) The bacteriological examinations should be comparable among the various diagnostic groups. Certain cases were excluded for this reason.

Therefore, the cases included in the present study are not strictly the same as those included in other reports based upon the same series of observations. Furthermore, differences in classification as to diagnosis exist between the present and other reports. These differences were minor, however, and will not be described in detail.

Cases of acuto respiratory disease included in this presentation are grouped into the following classes:

1. Undifferentiated acute respiratory disease (ARD). This diagnosis was one arrived at by exclusion of the following additional categories.

2. Streptococcal infections, as demonstrated by the development of streptococcal antibodies (37, 38). The great majority of these patients presented pharyngeal exudate.

3. Exudativo pharyngitis without streptococcal antibodies: a) With beta-hemolytic streptococci in first throat culture. b) Without beta-hemolytic streptococci in first throat culture.

4. Influenza A, with a fourfold or greater rise in antibody titer. This class was employed only during the epidemic of 1943–44. Although a few cases developed antibodies to influenza at other times (39), these serological results were ignored.

5. Primary atypical pneumonia.

RESULTS

Relationship of bacteriology to minor illness in platoon studies

Two methods were used to examine the association between the bacteria in throat cultures and the presence or absence of minor respiratory illness or a "cold", as indicated by the informant. The first method of analysis considered whether or not the bacterial flora of those individuals with a newly developed infection differed from that of the rest of the platoon. The second method of analysis considered whether or not the bacterial flora of the platoon as a whole varied in relation to the general prevalence of minor respiratory illnesses in that platoon.

A new respiratory illness was defined as one where an individual's record showed that he had denied having a cold one week, but claimed to have one the following week. He was considered to have had a fresh illness at the time of the culture corresponding to the positive entry. The definition of a new illness, then, did not depend on memory of the individual but on his answers to weekly questioning.

An obvious method of analysis would be to compare, week by week, the bacterial flora of those with new illness and the flora of the well soldiers. This comparison was precluded because the number of new respiratory infections each week was small. Neither was it possible to compare the average bacterial flora as determined over the whole period of each platoon study with that of the new illnesses, because of the wide variations in carrier rates which occurred from week to week. These limitations were avoided by summarizing the data on the basis of total carrier rates adjusted for date of culture. Such adjusted rates allow for differences in the weekly carrier rates of the platoon as a whole.

In calculating the adjusted rates for each organism, the number of new cases of minor illness for a given interview was multiplied by the total platoon carrier rate for that week, to determine the expected number of carriers among those

with new illnesses. The expected numbers for each week were added. The total number of expected carriers (Table 1, Col. 4) divided by the total number of new illnesses (Table 1, Col. 2) resulted in an expected carrier rate (Col. 6). This rate is the percentage of individuals with new illnesses who would be expected to harbor the organism if its presence were independent of new illnesses. The expected carrier rate may be compared directly with the observed rate among these individuals (Col. 5).

Table 1 summarizes the observations in all the platoons studied. This includes nine platoons with respect to the beta-hemolytic streptococcus, and six platoons for the other organisms. The first column showing the total number of cultures and interviews (see footnotes, Table 1), is included only to indicate the stability of the rates presented. For each of the five organisms the agreement

TABLE 1

Observed and expected carrier rates for each of five organisms in individuals with new illnesses —platoon studies

	TOTAL NUMBER CULTURED* (1)	NEW ILLNESSES				
		Number with new colds† (2)	Observed number with organism (3)	Expected number with organism (4)	Observed carrier rate (5)	Expected carrier rate (6)
					per cent	*per cent*
Beta-hemolytic streptococcus	4760	383	45	46	11.7	12.0
Staph. aureus	3727	303	32	27	10.6	8.9
Pneumococcus	3680	300	137	136	45.7	45.3
H. influenzae	3727	303	207	212	68.3	70.0
H. hemolyticus	3727	303	144	156	47.5	51.5

* At periods when the distinction of new colds could be made; i.e. beginning with the second interview.

† Included only when bacteriology and history both adequate.

between observed and expected carrier rates was very close. Therefore, no association between new illnesses and bacterial flora was demonstrated.

It is entirely possible that while the onsets of illnesses were not associated with a peculiar bacterial flora, a relationship might be found between changes in the general level of respiratory illness and the carrier rates for various organisms in the platoon as a whole. For example, an organism might become generally more prevalent but result in a new illness in only a small proportion of the affected individuals. Again, an organism might not be unduly prevalent soon after the onset of illness, but tend to become more prevalent in individuals who had had symptoms for longer than a week.

Relationships such as these if they existed should be evident in figure 1, which presents data regarding the total prevalence of minor respiratory illnesses and the corresponding carrier rates for each organism. The results for all the platoons which were studied are presented except for the three in which only strepto-

cocci and pneumococci were sought, and which were observed concurrently with the last three platoons diagrammed.

For none of the organisms is there evident a consistent relationship such as might be expected if a major portion of the illnesses were due to one of the specific organisms considered, or if minor respiratory illnesses resulted in a change in flora. There are instances of apparent parallelism between the carrier rate and prevalence of illness but apparent parallelism is bound to occur where so many series of observations are examined. For example, in the last platoon plotted, the prevalence of *H. influenzae* is roughly parallel to that of illness, but a contradictory situation is found in some of the other platoons. A number of

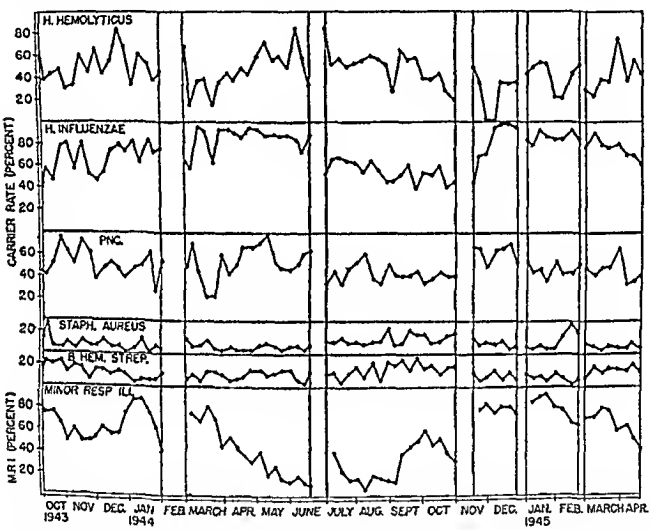


FIG. 1. PREVALENCE OF MINOR RESPIRATORY ILLNESS AND VARIOUS ORGANISMS, AS DETERMINED BY WEEKLY INTERVIEWS AND THROAT CULTURES. PLATOON STUDIES

such instances of parallelism may be seen in figure 1, the number depending upon the imagination of the examiner, but there is no consistent relationship. It cannot be denied that some of the apparent associations may be real, but it would appear very unlikely that over the whole period any one of the organisms was related, etiologically or otherwise, to a large portion of the minor respiratory illnesses.

Variation in carrier rates as determined in the platoon studies and in the studies of human volunteers

Carrier rates for each of the five organisms studied varied without relationship to the occurrence of minor respiratory illness. This was true both in the platoon

studies where cultures were taken at intervals of approximately one week, and in the studies with human volunteers (32) where the cultures were obtained more frequently.

The carrier rates in the platoons have been shown in Figure 1. They are summarized in Tables 2–6, which show frequency distributions of the rates,

TABLE 2

Carrier rates for beta-hemolytic streptococcus as determined by repeated cultures

CARRIER RATE	PLATOONS									HUMAN VOLUNTEERS	
	Oct. 43 Feb. 44	Feb. 44 June 44	July 44 Oct. 44	Nov. 44 Dec. 44		Jan. 45 Feb. 45		Feb. 45 Apr. 45		May–July 1945	July–Aug. 1945
per cent											
0–4	1*	2	1	—	1	2	2	—	3	2	2
5–9	4	5	2	4	4	5	1	1	5	1	5
10–14	6	8	4	3	2	1	2	5	—	5	9
15–19	3	3	7	—	—	—	3	2	—	6	7
20–24	4	—	2	—	—	—	—	—	—	8	1
25–29	—	—	2	—	—	—	—	—	—	2	—
Total....	18	18	18	7	7	8	8	8	8	24	24

* Figures indicate the number of times the indicated carrier rates were observed.

TABLE 3

Carrier rates for Staphylococcus aureus *as determined by repeated cultures*

CARRIER RATE	PLATOONS						HUMAN VOLUNTEERS	
	Oct. 43 Feb. 44	Feb. 44 June 44	July 44 Oct. 44	Nov. 44 Dec. 44	Jan. 45 Feb. 45	Feb. 45 Apr. 45	May–July 1945	July–August 1945
per cent								
0–4	3*	6	—	1	4	6	13	21
5–9	9	9	4	3	1	2	8	3
10–14	5	3	8	3	1	—	2	—
15–19	—	—	4	—	1	—	1	—
20–24	—	—	2	—	1	—	—	—
25–29	1	—	—	—	—	—	—	—
Total...	18	18	18	7	8	8	24	24

* Figures indicate the number of times the indicated carrier rates were observed.

i.e., in how many of the culture periods carrier rates were less than 5 per cent, 5 to 9 per cent, etc. These rates usually are based on between 50 and 60 cultures.

Similar information for the volunteers is presented in Figure 2[4] and in Tables 2–6. In order to include only rates which are approximately comparable, certain days' results are excluded from the distribution of Tables 2–6. On June

[4] Also indicated on figure 2 are the dates on which inoculations were given. No time sequences relating inoculation to changes in bacterial flora are evident (32).

TABLE 4

Carrier rates for pneumococcus as determined by repeated cultures

CARRIER RATE	PLATOONS						HUMAN VOLUNTEERS	
	Oct. 43 Feb. 44	Feb. 44 June 44	July 44 Oct. 44	Nov. 44 Dec. 44	Jan. 45 Feb. 45	Feb. 45 Apr. 45	May-July 1945	July-Aug. 1945
per cent								
20–24	—	2*	—	—	—	—	—	—
25–29	1	—	—	—	—	—	2	—
30–34	—	—	4	—	1	2	1	—
35–39	2	—	3	—	—	2	2	—
40–44	2	2	7	—	4	—	3	2
45–49	3	3	1	—	—	3	2	2
50–54	5	3	2	2	3	—	5	6
55–59	—	1	1	—	—	—	5	3
60–64	3	2	—	2	—	1	4	4
65–69	—	3	—	3	—	—	—	5
70–74	1	1	—	—	—	—	—	2
75–79	1	1	—	—	—	—	—	—
Total...	18	18	18	7	8	8	24	24

* Figures indicate the number of times the indicated carrier rates were observed.

TABLE 5

Carrier rates for H. influenzae *as determined by repeated cultures*

CARRIER RATE	PLATOONS						HUMAN VOLUNTEERS	
	Oct. 43 Feb. 44	Feb. 44 June 44	July 44 Oct. 44	Nov. 44 Dec. 44	Jan. 45 Feb. 45	Feb. 45 Apr. 45	May-July 1945	July-Aug. 1945
per cent								
5–9	—	—	—	—	—	—	2*	1
10–14	—	—	—	—	—	—	4	5
15–19	—	—	—	—	—	—	2	4
20–24	—	—	—	—	—	—	2	6
25–29	—	—	—	—	—	—	9	4
30–34	—	—	—	—	—	—	2	3
35–39	—	—	1	—	—	—	3	—
40–44	1	—	2	1	—	—	—	1
45–49	2	—	2	—	—	—	—	—
50–54	2	—	5	—	—	—	—	—
55–59	2	1	2	—	—	—	—	—
60–64	1	2	5	—	—	1	—	—
65–69	—	—	1	1	—	2	—	—
70–74	3	1	—	1	—	—	—	—
75–79	3	—	—	—	1	4	—	—
80–84	4	1	—	—	4	—	—	—
85–89	—	8	—	—	1	1	—	—
90–94	—	4	—	2	2	—	—	—
95–99	—	1	—	2	—	—	—	—
Total...	18	18	18	7	8	8	24	24

studies where cultures were taken at intervals of approximately one week, and in the studies with human volunteers (32) where the cultures were obtained more frequently.

The carrier rates in the platoons have been shown in Figure 1. They are summarized in Tables 2–6, which show frequency distributions of the rates,

TABLE 2

Carrier rates for beta-hemolytic streptococcus as determined by repeated cultures

CARRIER RATE	PLATOONS									HUMAN VOLUNTEERS	
	Oct. 43 Feb. 44	Feb. 44 June 44	July 44 Oct. 44	Nov. 44 Dec. 44		Jan. 45 Feb. 45		Feb. 45 Apr. 45		May–July 1945	July–Aug. 1945
per cent											
0–4	1*	2	1	—	1	2	2	—	3	2	2
5–9	4	5	2	4	4	5	1	1	5	1	5
10–14	6	8	4	3	2	1	2	5	—	5	9
15–19	3	3	7	—	—	—	3	2	—	6	7
20–24	4	—	2	—	—	—	—	—	—	8	1
25–29	—	—	2	—	—	—	—	—	—	2	—
Total....	18	18	18	7	7	8	8	8	8	24	24

* Figures indicate the number of times the indicated carrier rates were observed.

TABLE 3

Carrier rates for Staphylococcus aureus *as determined by repeated cultures*

CARRIER RATE	PLATOONS						HUMAN VOLUNTEERS	
	Oct. 43 Feb. 44	Feb. 44 June 44	July 44 Oct. 44	Nov. 44 Dec. 44	Jan. 45 Feb. 45	Feb. 45 Apr. 45	May–July 1945	July–August 1945
per cent								
0–4	3*	6	—	1	4	6	13	21
5–9	9	9	4	3	1	2	8	3
10–14	5	3	8	3	1	—	2	—
15–19	—	—	4	—	1	—	1	—
20–24	—	—	2	—	1	—	—	—
25–29	1	—	—	—	—	—	—	—
Total...	18	18	18	7	8	8	24	24

* Figures indicate the number of times the indicated carrier rates were observed.

i.e., in how many of the culture periods carrier rates were less than 5 per cent, 5 to 9 per cent, etc. These rates usually are based on between 50 and 60 cultures.

Similar information for the volunteers is presented in Figure 2[4] and in Ta 2–6. In order to include only rates which are approximately c certain days' results are excluded from the distribution of Tables 2–6. On

[4] Also indicated on figure 2 are the dates on which inoculations were given. N sequences relating inoculation to changes in bacterial flora are evident (32).

TABLE 4

Carrier rates for pneumococcus as determined by repeated cultures

CARRIER RATE	PLATOONS						HUMAN VOLUNTEERS	
	Oct. 43 Feb. 44	Feb 44 June 44	July 44 Oct. 44	Nov. 44 Dec. 44	Jan. 45 Feb 45	Feb. 45 Apr. 45	May–July 1945	July–Aug. 1945
per cent								
20–24	—	2*	—	—	—	—	—	—
25–29	1	—	—	—	—	—	2	—
30–34	—	—	1	—	1	2	1	—
35–39	2	—	3	—	—	2	2	—
40–44	2	2	7	—	4	—	3	2
45–49	3	3	1	—	—	3	2	2
50–54	5	3	2	2	3	—	5	6
55–59	—	1	1	—	—	—	5	3
60–64	3	2	—	2	—	1	4	4
65–69	—	3	—	3	—	—	—	5
70–74	1	1	—	—	—	—	—	2
75–79	1	1	—	—	—	—	—	—
Total	18	18	18	7	8	8	24	24

* Figures indicate the number of times the indicated carrier rates were observed.

TABLE 5

Carrier rates for H. influenzae *as determined by repeated cultures*

CARRIER RATE	PLATOONS						HUMAN VOLUNTEERS	
	Oct. 43 Feb. 44	Feb. 44 June 44	July 44 Oct. 44	Nov. 44 Dec. 44	Jan. 45 Feb. 45	Feb. 45 Apr. 45	May–July 1945	July–Aug. 1945
per cent								
5–9	—	—	—	—	—	—	2*	1
10–14	—	—	—	—	—	—	4	5
15–19	—	—	—	—	—	—	2	4
20–24	—	—	—	—	—	—	2	6
25–29	—	—	—	—	—	—	9	4
30–34	—	—	—	—	—	—	2	3
35–39	—	—	1	—	—	—	3	—
40–44	1	—	2	1	—	—	—	1
45–49	2	—	2	—	—	—	—	—
50–54	2	—	5	—	—	—	—	—
55–59	2	1	2	—	—	—	—	—
60–64	1	2	5	—	—	—	—	—
65–69	—	—	1	1	—	1	—	—
70–74	3	1	—	1	—	2	—	—
75–79	3	—	—	—	1	4	—	—
80–84	4	1	—	—	4	—	—	—
85–89	—	8	—	—	1	1	—	—
90–94	—	4	—	2	2	—	—	—
95–99	—	1						

26 and July 14 many of the plates were contaminated, and, therefore, the results for these days are not included. On July 4, 6, 8, and 10, many of the volunteers were not observed because at this time the group was reforming for the second experiment. Therefore, these rates also are excluded. Each of the remaining carrier rates is based on 35 to 40 cultures for the first time period (except one pneumococcus rate based on 34), and 37 to 43 cultures for the second time period.

TABLE 6

Carrier rates for H. hemolyticus *as determined by repeated cultures*

CARRIER RATE	PLATOONS						HUMAN VOLUNTEERS	
	Oct. 43 Feb. 44	Feb. 44 June 44	July 44 Oct. 44	Nov. 44 Dec. 44	Jan. 45 Feb. 45	Feb. 45 Apr. 45	May–July 1945	July–Aug. 1945
per cent								
0–4	—	—	—	2	—	—	—	—
5–9	—	—	—	—	—	—	1*	—
10–14	—	—	—	—	—	—	—	—
15–19	—	2	—	—	—	—	3	—
20–24	—	—	1	—	2	1	1	1
25–29	—	—	2	—	—	1	3	—
30–34	3	2	—	2	—	—	1	1
35–39	2	3	2	2	—	3	2	1
40–44	2	2	1	—	2	1	4	2
45–49	3	1	1	1	1	—	—	2
50–54	2	2	5	—	3	—	2	2
55–59	1	2	4	—	—	1	3	3
60–64	3	1	1	—	—	—	2	2
65–69	1	1	—	—	—	—	2	2
70–74	—	1	—	—	—	1	—	4
75–79	—	—	—	—	—	—	—	2
80–84	1	1	1	—	—	—	—	1
85–89	—	—	—	—	—	—	—	1
Total...	18	18	18	7	8	8	24	24

* Figures indicate the number of times the indicated carrier rates were observed.

It is evident, from the data presented, that large differences in carrier rates occurred without apparent cause. The reasons for these variations were not sought except to determine whether or not they were related to respiratory disease. They are doubtlessly due both to gross technical limitations (35) and to true changes in the bacterial flora of the individuals concerned. Regardless of the reasons, they show that within a group of men, the carrier rate, as determined, varied markedly within a short period of time. The carrier rate of *H. hemolyticus* was determined as zero on one day and 35 per cent a week later, as shown in one of the platoon studies; it went from 68 per cent to 18 per cent two

days later during the human volunteer experiments. Each of these changes is based on repeated cultures of the same men.

When differences such as these occur within population groups, the problem of seeking a causal relationship between one of these organisms and respiratory diseases is not simple. Judgment cannot be based on a significant difference, as determined by the criteria of simple sampling, between the sick and well individuals, for by these very criteria the well group might be judged to have a significantly different carrier rate than it had had a few days previously.

Differences in carrier rates of the degree shown in tables 2–6 occurred for no attributable reason in serial cultures from the same individuals. In contrasting

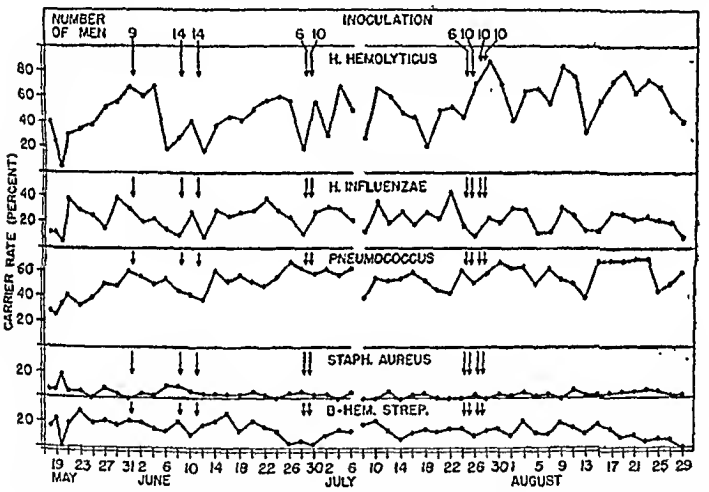


FIG. 2. CARRIER RATES FOR VARIOUS ORGANISMS AS DETERMINED BY THROAT CULTURES TAKEN EVERY SECOND DAY. MEN IN ISOLATION

Arrows indicate the dates on which inoculations were given and the the number of men inoculated

different groups of individuals even greater variations must occur before a causal relationship can be deduced. Striking evidence of this may be seen by comparing the general level of *H. influenzae* (Table 5) in the volunteer experiments with that in the platoons. No explanation for these differences is apparent.

BACTERIOLOGICAL OBSERVATIONS OF HOSPITALIZED PATIENTS

The primary purpose of studying the bacteriological findings of the hospitalized patients was to determine whether or not a characteristic flora was associated with ARD. No truly suitable control observations were made in connection with the studies of these cases. As stated previously, the basic population from which patients were selected included the platoon which was being studied

concurrently. But the platoons were not ideal control groups, and their usefullness as such is very limited, for they represented only a small section of the

TABLE 7

Carrier rates for beta-hemolytic streptococcus, as determined in platoon studies and for hospital admissions

	DATE											
	10/9/43–2/5/44		2/22–6/22/44		7/1–11/2/44		11/14–12/30/44		1/2–2/24/45		2/25–4/22/45	
	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive
Platoon 1	1059	13	979	10	958	16	386	8	488	11	481	5
Platoon 2	0	—	0	—	0	—	377	9	498	6	481	13
Total platoons	1059	13	979	10	958	16	763	9	986	8	962	9
Hospitalized patients:												
1) ARD	161	6	216	13	10	0	14	7	173	6	129	15
2) Strep. antibody	17	100	59	81	0	—	5	80	3	67	7	100
3) Exudate, no antibody	22	23	97	25	2	0	5	20	31	13	16	12
a) With strep	5	100	24	100	0	—	1	100	4	100	2	100
b) No strep	17	0	73	0	2	0	4	0	27	0	14	0
4) Influenza	79	10	0	—	0	—	0	—	0	—	0	—
5) Atypical pneumonia	27	11	36	19	19	11	5	0	14	14	10	10

TABLE 8

Carrier rates for Staphylococcus aureus *as determined in platoon studies and for hospital admissions*

	DATE											
	10/9/43–2/5/44		2/22–6/22/44		7/1–11/2/44		11/14–12/30/44		1/2–2/24/45		2/25–4/22/45	
	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive
Platoon	1059	8	979	7	958	14	377	8	498	9	481	5
Hospitalized patients:												
1) ARD	161	6	216	7	10	10	14	0	172	2	129	4
2) Strep. antibody	17	12	59	5	0	—	5	20	3	0	7	0
3) Exudate, no antibody	22	0	97	8	2	50	5	0	31	0	16	0
a) With strep	5	0	24	12	0	—	1	0	4	0	2	0
b) No strep	17	0	73	7	2	50	4	0	27	0	14	0
4) Influenza	79	14	0	—	0	—	0	—	0	—	0	—
5) Atypical pneumonia	27	19	36	8	19	5	5	0	14	0	10	0

total population from which the hospitalized patients came. In view of the marked short-time variations observed in carrier rates demonstrated above,

suitable control observations would necessarily require the frequent culturing of a large number of men scattered throughout the population.

In the absence of adequate controls two sets of comparisons have been made. The first is that of the platoons with the hospitalized patients studied at the same time. The second compares the bacteriology of the various diagnostic classes of hospitalized patients. The two comparisons complement each other to a considerable degree.

Tables 7–11 present the bacteriological results of hospitalized patients and the average carrier rates in the platoons. There is no evidence that the bacterial flora was altered in patients with ARD. During two periods, *H. hemolyticus* was markedly more prevalent in the ARD patients than in the corresponding

TABLE 9

Carrier rates for pneumococcus, as determined in platoon studies and for hospital admissions*

	DATE											
	10/9/43–2/5/44		2/22–6/22/44		7/1–11/2/44		11/14–12/30/44		1/2–2/24/45		2/25–4/22/45	
	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive
Platoon	1017	52	976	53	959	42	377	61	492	45	479	43
Hospitalized patients:												
1) ARD	130	37	211	36	8	62	13	54	167	43	129	53
2) Strep. antibody	15	27	57	19	0	—	5	20	3	33	7	0
3) Exudate, no antibody	18	33	92	28	2	50	5	40	31	52	16	56
a) With strep.	4	50	22	32	0	—	1	0	4	75	2	0
b) No strep.	14	29	70	27	2	50	4	50	27	48	14	64
4) Influenza	74	46	0	—	0	—	0	—	0	—	0	—
5) Atypical pneumonia	25	40	35	34	19	32	5	40	14	43	9	78

* Includes only those cultures where both blood agar plates and mouse were examined.

platoon studies. However, during both of these periods, the other diagnostic groups also showed this organism more frequently than did the platoon studies. These two facts taken together probably mean that the particular men in those platoons tended to carry *H. hemolyticus* less frequently than those in the majority of the platoons making up the population for the hospital study rather than that the organism was unduly associated with ARD. In the absence of more precise knowledge of the specific carrier rates, there is no basis for claiming or denying an etiological relationship. Because of the lack of consistently higher carrier rates of *H. hemolyticus* in cases of ARD in the other time periods, however, the more probable explanation is the one presented.

The reverse argument may be presented regarding the pneumococcus. Between February 22 and June 22, 1944, the pneumococcus was less prevalent in the ARD group than in the corresponding platoons. But it was even less prevalent in the other diagnostic groups. The consistent lack of similar findings

in the other time periods probably reflects the fact that the platoon was a poor sample of the population rather than that the pneumococcus was suppressed in ARD.

TABLE 10

Carrier rates for H. influenzae *as determined in platoon studies and for hospital admission*

	DATE											
	10/9/43–2/5/44		2/22–6/22/44		7/1–11/2/44		11/14–12/30/44		1/2–2/24/45		2/25–4/22/45	
	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive
Platoon	1059	60	979	83	958	54	377	81	498	85	481	75
Hospitalized patients:												
1) ARD	161	73	216	79	10	60	14	64	172	80	129	88
2) Strep. antibody	17	65	59	68	0	—	5	20	3	100	7	57
3) Exudate, no antibody	22	82	97	66	2	50	5	80	31	77	16	75
a) With Strep	5	80	24	71	0	—	1	0	4	100	2	100
b) No strep	17	82	73	64	2	50	4	100	27	74	14	71
4) Influenza	79	53	0	—	0	—	0	—	0	—	0	—
5) Atypical pneumonia	27	63	36	78	19	68	5	60	14	71	10	70

TABLE 11

Carrier rates for H. hemolyticus *as determined in platoon studies and for hospital admissions*

	DATE											
	10/9/43–2/5/44		2/22–6/22/44		7/1–11/2/44		11/14–12/30/44		1/2–2/24/45		2/25–4/22/45	
	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive	Number cultures	Per cent positive
Platoon	1059	50	979	46	958	49	377	26	498	42	481	41
Hospitalized patients:												
1) ARD	161	70	216	44	10	50	14	21	172	45	129	66
2) Strep. antibody	17	53	59	19	0	—	5	0	3	33	7	29
3) Exudate, no antibody	22	73	97	37	2	50	5	20	31	42	16	75
a) With strep	5	60	24	38	0	—	1	0	4	25	2	100
b) No strep	17	76	73	37	2	50	4	25	27	44	14	71
4) Influenza	79	61	0	—	0	—	0	—	0	—	0	—
5) Atypical pneumonia	27	59	35	34	19	32	5	20	14	21	10	50

The results for cases of primary atypical pneumonia were similar to those for ARD. Inasmuch as atypical pneumonia is due to a filtrable agent (40), it is not surprising that no alteration in the pharyngeal flora was encountered.

By contrast there were two groups of patients whose cultural results appear to be different both from those of the other diagnostic groups from the platoon

subjects. Those who developed streptococcal antibodies showed beta-hemolytic streptococci more frequently than did any other group. This, of course, was to be anticipated. Patients with exudate but no streptococcal antibodies also, in general, harbored the beta-hemolytic streptococci more frequently than did the other groups. The latter finding may be explained by the fact that non-streptococcal exudate was found more frequently in patients with tonsils than in patients without tonsils, and individuals with tonsils harbor beta-hemolytic streptococci more frequently than those without tonsils, regardless of the presence or absence of respiratory illness.

DISCUSSION

An investigation of the relationship of infection and the aerobic bacterial flora of the upper respiratory tract is complicated by two factors. First, it is necessary to determine not only whether unusual organisms are present during illness, but also whether the common organisms are detectable in infected individuals more frequently than in normal persons. Secondly, it is quite likely that no single etiological agent is responsible for all of the minor respiratory infections that clinically appear to be variants of a single disease entity. Certainly the beta-hemolytic streptococcus and the viruses of primary atypical pneumonia and influenza at times produce illnesses which are, in the absence of laboratory tests, indistinguishable from cases of unknown etiology. It has been demonstrated recently (32) that there are at least two filtrable agents producing mild respiratory diseases which might clinically be confused with each other. As entities become defined and made distinguishable by laboratory methods from the large mass of undifferentiatied disease, there remains a more homogeneous group for further study. Periodically, therefore, the possible bacteriological relationships in the residua should be re-investigated. When cases of known etiology are eliminated, the group which *might* be caused by bacteria as yet unidentified, becomes better defined, and it becomes more likely that any bacteriological differences which exist may come to light.

In spite of progress in differential diagnosis, however, the difficulties of determining whether the flora of ill persons differs from that of well individuals will remain. This has been recognized by many workers, whose approaches to the problem have been quite diverse.

One class of studies includes those which have been made in conjunction with attempts to transmit colds to humans. In two of these experiments (13, 17) no significant differences in bacterial flora were found between preinoculation cultures and those taken from the same individuals after the onset of the induced infections. However, in chimpanzees which were studied similarly (13) changes in flora were noted almost invariably. The alterations in flora were not the same in all animals, but might consist of a sudden appearance of pneumococci in the nose or throat in some animals, or a spread of *H. influenzae* or hemolytic streptococci to the nose in others. Robertson and Groves (6) noted a marked reduction in the bacterial flora, with one organism predominating, during the early stages of infection and a marked increase in flora, with the predominance of

one organism, usually *Staphylococcus albus*, 36 to 48 hours after onset. Similar observations by the Commission on Acute Respiratory Diseases showed no changes which could be related to illness. These findings, while not completely in agreement with one another, are consistent in that they incriminate no one organism.

Studies in which serial cultures have been taken from individuals in health and during respiratory infections acquired in the normal course of their lives form another class. Bloomfield (41) pointed out the advantages of this method of investigation, and reported that the transient flora was "distinctly richer and more varied than that found in our series of controls" (4). He offered as an explanation the possibility that "the disturbance of the mucous membranes during the cold allows a general increase in the activity of bacterial growth on these surfaces". Bloomfield (4, 41–45), like Jordon et al (5), emphasized the variation which occurred in the normal throat from time to time. Jordon concluded that variations noted during colds were no greater than those observed during periods of health.

Other workers (2, 3, 7–12, 14–16, 18–31), using serial cultures or comparing cultures from persons with colds with those from normal persons have reached various conclusions. Most of these can be summarized either as concluding that no significant changes in flora were associated with infection, or that, although a change in occurrence or predominance in growth did take place, this change might be in any one of a variety of organisms. Hodges, MacLeod and Bernhard (46), in a well controlled study at an army air force school experiencing an unusually high incidence of pneumococcal pneumonia, showed that the pneumococcal carrier rate did not bear a close relationship to the incidence of non-bacterial respiratory disease. There seems to be a fairly general opinion that the nasal flora is increased quantitatively during a respiratory illness, but no agreement as to what happens in the throat and nasopharynx.

The present observations indicate no significant alterations in flora in throat cultures concurrent with illness. Evidence reported elsewhere (35, V) showed little difference between the results of pharyngeal and nasopharyngeal cultures. No nasal cultures were taken in the present series of studies.

As emphasized by Bloomfield (41), the most efficient method of studying the relationship of minor respiratory disease and the bacterial flora of the respiratory tract is by taking serial cultures before, during, and after colds, employing the same subjects repeatedly over a period of time. In the present report this has been done in two ways. Human volunteers were subjected to inoculation with infectious material, and bacteriological observations were made at two day intervals throughout prolonged pre- and post-inoculation periods. No changes in flora were noted during illness which were greater than those seen in the same individuals before illness or in other individuals not inoculated. In a similar manner, several platoons of soldiers were cultured at weekly intervals. No evidence was found that changes in bacterial flora occurred in relationship to the onset of colds.

In both of these studies, however, marked variations in carrier rates were en-

countered in successive cultures. Much of this variation was due to technical limitations in cultural methods (35). However, a large part probably is due to true changes in flora. Regardless of the reason, these variations indicate the necessity for adequate control observations. It is believed that these were obtained in the platoon and volunteer studies.

In a large scale study such as was done with hospitalized patients, however, adequate controls are obtained with difficulty, and as carried out, the study was inadequately controlled. The platoons failed, in that they represented only a small segment of the population from which the study cases came. That such a segment is not satisfactory is shown by the fact that pneumococci of specific types were demonstrated to spread within a platoon, which would tend to increase the carrier rate in the control group. Such an event could, and probably does, occur with other organisms which cannot be so accurately identified. If these carrier epidemics occur either more or less in the control platoon than in the other platoons making up the population groups, the control is then biased. Similar spreads have been reported in a children's institution (epidemiologically quite similar to a barracks) for diphtheria bacilli and sulfonamide-resistant strains of pneumococci (47).

For this reason, a supplementary control group, probably more representative of the total population than is true of the platoon groups, was used. This consisted of hospitalized admissions with clinical or laboratory characteristics differing from those (ARD) primarily considered in this paper. Using both of these sets of control observations, it appeared that the cases of undifferentiated acute respiratory disease had no distinct bacteriological characteristics.

Therefore, it may be concluded that uncomplicated ARD was not associated with detectable differences in throat flora.

SUMMARY

Serial throat cultures were obtained weekly from several platoons of army recruits. Considerable variation was observed in the carrier rates of several organisms determined from these cultures. These variations were not related to the development or to the general prevalence of minor respiratory illness. Similar observations made on a group of men in isolation also showed marked variation in carrier rates for no apparent reason.

The results of throat cultures of men hospitalized for undifferentiated acute respiratory disease (ARD) and influenza revealed no differences which could be associated with their illnesses, in contrast to the findings in true β-hemolytic streptococcal infections.

ACKNOWLEDGMENTS

The Commission on Acute Respiratory Diseases wishes to thank the following officers for their active support which made these studies possible: Major General D. C. Cubbison, Brigadier General J. T. Kennedy, Brigadier General H. C. Coburn, Jr., Colonel G. D. Chunn, Colonel J. N. Williams, Colonel R. J. Horr, Colonel W. B. Daniels, Lieutenant Colonel F. W. Bryant, Lieutenant

Colonel J. M. Kinsman, and the commanding officers and their staffs of the regiments, battalions, and batteries of the FA-RTC.

The following men have rendered valuable assistance during the course of the studies: Major G. R. Newton, Personnel Adjutant, FA-RTC; Major R. L. Siegel, Surgeon, FA-RTC; Major B. E. Moore, Surgeon, FA-RTC; Major W. J. McVey, Classification Officer, FA-RTC; Major A. M. Sands, Chief, Sanitation Branch, Fort Bragg; Captain D. Butterfield, Personnel Adjutant, FA-RTC; Captain, L. M. Bowen, Registrar, Regional Hospital; Captain D. L. Martin, Registrar, Regional Hospital; and their staff officers and enlisted men. The medical officers on the wards, in the X-ray Service and in the Receiving Office have cooperated fully in this study.

The Commission on Acute Respiratory Diseases takes pleasure in acknowledging the assistance of the technical staff of the Laboratory: Capt. Aaron Ignatow, M.A.C.; First Lt. Walter A. Mickle, Sn.C.; First Lt. Thomas J. Oliver, Sn.C.; First Lt. Ralph Robinson, Sn.C.; Cpl. Alexander Adler; T/Sgt. Louis P. Codifer; Cpl. Victor Culver; S/Sgt. Howard E. Duke; Sgt. David O. Foltz; T/Sgt. Eli Gold; Sgt. Curtis Hoover; Sgt. Melvin H. Kaplan; Sgt. Gerald J. Leuty; S/Sgt. Robert W. Mott; Pfc. Woonyong Park; S/Sgt. Willard W. Skatrud; Sgt. Frank Sullivan; Doris V. Brown; Ruth Chase; Dorothy Concorida; Mary E. Deaton; Sybil Harlam; Eleanor F. Hoenig; Carolyn Kaldus; Rosabelle M. Kiernan; Sara A. Marshall; Dorothy Mickle; Barbara A. Mulliken; Jessie P. Neeley; Irene A. Salamandra; Betsy Smith; Mable Smith; Sally Taylor; Bettie L. Wooten.

REFERENCES

1. Mudd, S., Grant, S. B., and Goldman, A., The etiology of acute inflammations of the nose, pharynx, and tonsils. Ann. Otol., Rhin., and Laryng., 30: 1, 1921.
2. Shibley, G. S., Hanger, F. M., and Dochez, A. R., Studies in the common cold. I. Observations of the normal bacterial flora of nose and throat with variations occurring during colds. J. Exper. Med., 43: 415, 1926.
3. Williams, A. W., Nevin, M., and Gurley, C. R., Studies on acute respiratory infections. I. Methods of demonstrating micro-organisms, including "Filtrable Viruses", from upper respiratory tract in "Health", in "Common Colds" and in "Influenza" with the object of discovering "Common Strains". J. Immunol., 6: 5, 1921.
4. Bloomfield, A. L., Variations in the bacterial flora of the upper air passages during the course of common colds. Bull. Johns Hopkins Hosp., 32: 121, 1921.
5. Jordan, E. O., Norton, J. F., and Sharp, W. B., The Common cold. Influenza studies XIV. J. Infect. Dis., 33: 416, 1923.
6. Robertson, R. C., and Groves, R. L., Experimental human inoculations with filtered nasal secretions from acute coryza. J. Infect. Dis., 34: 400, 1924.
7. Noble, W. C., Jr., Fisher, E. A., and Brainard, D. H., Studies of acute respiratory infections; comparison of aerobic flora of upper respiratory tract of persons in health and with colds. J. Prev. Med., 2: 105, 1928.
8. Bourn, J. M., Incidence of Pfeiffer's bacillus in throats during epidemic and interepidemic periods in Chicago. J. Prev. Med., 2: 441, 1928.
9. Shibley, G. S., Mills, K. C., and Dochez, A. R., Further consideration of transmissibility of human upper respiratory infections (common cold) to the ape. Proc. Soc. Exper. Biol. and Med. 27: 59, 1929.

10. Smillie, W. G., and Caldwell, E. L., Study of pneumonia in rural area in southern Alabama. J. Exper. Med., 50: 233, 1929.
11. Bunky, E. L., and Smillie, W. G., Nasopharyngeal flora in health and during respiratory disease in isolated communities in Alabama and Labrador. J. Exper. Med., 50: 643, 1929.
12. Dochez, A. R., Shibley, G. S., and Mills, K. C., Studies of etiology of common cold. J. A. M. A., 95: 1553, 1930.
13. Dochez, A. R., Shidley, G. S., and Mills, K. C., Studies in the common cold. IV. Experimental transmission of the common cold to anthropoid apes and human beings by means of a filtrable agent. J. Exper. Med., 52: 701, 1930.
14. Kneeland, Y., Jr., Studies in the common cold. III. The upper respiratory flora of infants. J. Exper. Med., 51: 617, 1930.
15. Blackburn, R. H., Boston, R. B., Gilmore, E. St. G., Lovell, R., Wilson, S. P., and Smith, M. M., Report on a study of the nasopharyngeal bacterial flora of a group of the Manchester population during the period July, 1925 to September 1927. Reports on Pub. Health and Med. Subjects, No. 58, 1930, Ministry of Health.
16. Milam, D. F., and Smillie, W. G., A bacteriological study of "colds" in an isolated tropical island (St. Johns, United States Virgin Islands, West Indies). J. Exper. Med., 53: 733, 1931.
17. Long, P. H., Doull, J. A., Bourn, J. M., and McComb, E., The etiology of acute upper respiratory infection (common cold). J. Exper. Med., 53: 447, 1931.
18. Webster, L. T., and Hughes, T. P., The epidemiology of pneumococcus infection. The incidence and spread of pneumococci in the nasal passages and throats of healthy persons. J. Exper. Med., 53: 535, 1931.
19. Webster, L. T., and Clow, A. D., The association of pneumococci, *Hemophilus influenzae* and *Streptococcus hemolyticus* with coryza, pharyngitis, and sinusitis in man. J. Exper. Med., 55: 445, 1932.
20. Bourn, J. M. *Hemophilus influenzae* in upper respiratory disease and in health, 1928–1930. Am. J. Hyg., 15: 64, 1932.
21. Kneeland, Y., Jr., and Daws, C. F., Studies in the common cold. V. The relationship of pathogenic bacteria to upper respiratory disease in infants. J. Exper. Med., 55: 735, 1932.
22. Dochez, A. R., Mills, K. C., and Kneeland, Y., Jr., Variation of *H. influenzae* during acute respiratory infection in the chimpanzee. Proc. Soc. Exper. Biol. and Med., 30: 314, 1932.
23. Paul, J. H., and Freese, H. L., An epidemiological and bacteriological study of the "common cold" in an isolated arctic community (Spitsbergen). Am. J. Hyg., 17: 517, 1933.
24. Bourn, J. M., Carpenter, H. M. and McComb, E., *Streptococcus haemolyticus* (beta) in the presence and absence of acute minor respiratory infection, 1928–1931. Am. J. Hyg., 17: 761, 1933.
25. Hoyle, L., The haemophilic bacteria of the upper respiratory tract. The appearance of virulent forms in relation to upper respiratory infections. J. Hyg., 34: 195, 1934.
26. Yardumian, K., and Lightener, E. L., Nasopharyngeal flora and some remarks as to their relation to common colds. J. Lab. and Clin. Med., 19: 877, 1934.
27. Straker, E., Hill, A. B., and Lovell, R., A study of the nasopharyngeal bacterial flora of different groups of persons observed in London and South-east England during the years 1930–37. Reports on Pub. Health and Med. Subjects, No. 90, 1939, Ministry of Health.
28. Cecil, R. L., Plummer, N., and Smillie, W. G., Sulfadiazine in the treatment of the common cold. J. A. M. A., 124: 8, 1944.

29. Kruse, W., Die erreger von Husten und Schnupfen, Munch. Med. Wchnschr., **61:** 1547, 1914.
30. Foster, G. B., Jr., The etiology of common colds. The probable role of a filterable virus as the causative factor: A preliminary note. J. A. M. A., **66:** 1180, 1916.
31. Foster, G. B., Jr., The etiology of common colds. The probable role of a filterable virus as the causative factor: with experiments on the cultivation of a minute micro-organism from the nasal secretion filtrates. J. Infect. Dis., **21:** 451, 1917.
32. Commission on Acute Respiratory Diseases., Experimental transmission of minor respiratory illness to human volunteers by filter-passing agents. J. Clin. Invest., **26:** 957 and 974, 1947.
33. Commission on Acute Respiratory Diseases., Clinical patterns of undifferentiated and other acute respiratory diseases in army recruits. Medicine, **26:** 333–394 (Dec.) 1947.
34. Commission on Acute Respiratory Diseases., Acute respiratory disease among new recruits. Am. J. Pub. Health, **36:** 439, 1946.
35. Commission on Acute Respiratory Diseases, Mickle, W. A., Oliver T. J., Robinson, R. L., and Plummer, N., Problems in determining the bacterial flora of the pharynx. I. Technique of examining a throat swab. II. The inadequacy of blood agar plates for indicating the relative proportions of different organisms inoculated simultaneously. III. The value of a selective medium, for the isolation of beta-hemolytic streptococci. IV. Studies on the technique of isolating pneumococci from throat cultures by mouse inoculation. V. Comparison of pharyngeal and nasopharyngeal cultures. VI. The single throat culture as an index of the bacterial flora of the respiratory tract. To be published.
36. Commission on Acute Respiratory Diseases and Commission on Air-Borne Infections., A study of the effect of oiled floors and bedding on the incidence of respiratory disease in new recruits. Am. J. Hyg., **43:** 120, 1946.
37. Commission on Acute Respiratory Diseases., Endemic exudative pharyngitis and tonsillitis. J. A. M. A., **125:** 1163, 1944.
38. Keith, J. D., and Carpenter, J., The diagnosis of haemolytic streptococcal infection in acute nasopharyngitis. Canad. J. Pub. Health, **37:** 127, 1946.
39. Commission on Acute Respiratory Diseases., Studies on endemic influenza. Unpublished data.
40. Commission on Acute Respiratory Diseases., The present status of the etiology of primary atypical pneumonia. Bull. New York Acad. Med., **21** (second series): 235, 1945.
41. Bloomfield, A. L., The serial quantitative method of culture in the study of respiratory disease. J. A. M. A., **77:** 187, 1921.
42. Bloomfield, A. L., The significance of bacteria found in the throats of healthy people. Bull. Johns Hopkins Hosp., **32:** 33, 1921.
43. Bloomfield, A. L., The mechanism of the bacillus carrier state with special reference to the Friedlander bacillus. Am. Rev. Tuberc., **4:** 847, 1921.
44. Bloomfield, A. L., The dissemination of bacteria in the upper air passages. II. The circulation of bacteria in the mouth. Bull. Johns Hopkins Hosp., **33:** 145, 1922.
45. Bloomfield, A. L., The significance of the influenza bacilli. Bull. Johns Hopkins Hosp., **33:** 172, 1922.
46. Hodges, R. G., MacLeod, C. M., and Bernhard, W. G., Epidemic pneumococcal pneumonia III. Pneumococcal carrier studies. Am. J. Hyg. **44:** 207, 1946.
47. Julianelle, L. A., and Siegel, M., The epidemiology of acute respiratory infections conditioned by sulfonamides. III. Effects of treatment of the organism and carrier of diphtheria. Ann. Int. Med., **22:** 21, 1945. V. Carrier epidemics of sulfonamide-resistant pneumococci. Am. J. Hyg., **41:** 228, 1945. VI. The epidemicity of subclinical pneumococcal infections. Am. J. Hyg., **42:** 214, 1945.

AUTHOR AND TITLE INDEX

Volumes 1–26

containing large amounts of ascorbic acid was good. Other places fell between the extremes seen on Guadalcanal and on Guam, and the overall average excretion was slightly below that found in the United States.

I. Diagnoses

As a result of the clinical and biochemical studies, no diagnoses were made among U. S. troops in the Pacific Theater of Operations of the specific deficiency

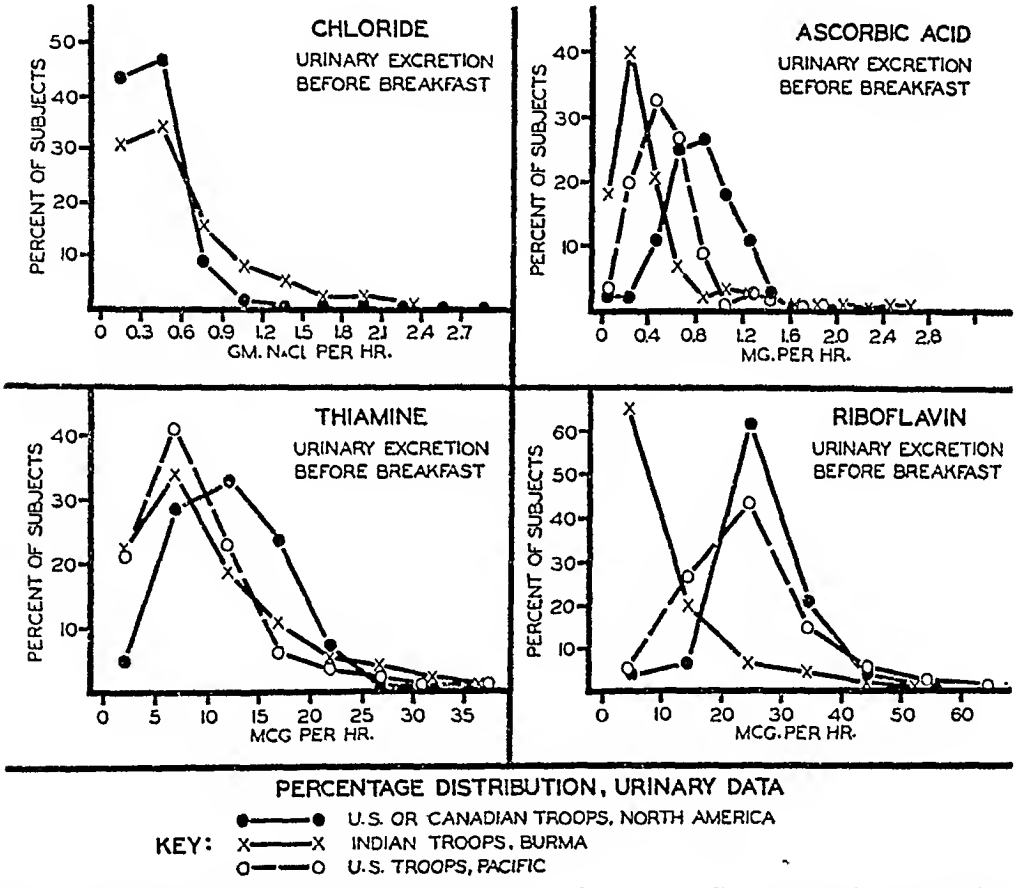


FIG. 2. PERCENTAGE DISTRIBUTION CURVES FOR DATA ON CHLORIDE, ASCORBIC ACID, THIAMINE AND RIBOFLAVIN EXCRETION IN SAMPLES OF URINE COLLECTED BEFORE BREAKFAST FROM U. S. TROOPS IN THE PACIFIC (300 MEN), INDIAN TROOPS IN BURMA (1000 MEN) AND U. S. INFANTRY IN COLORADO (600 MEN)

diseases scurvy, beri-beri, pellagra, xerophthalmia or "hunger edema." Some evidence was found of moderate caloric deficit in groups under stress of combat.

J. Dietary, Biochemical and Clinical Correlations

The relationships between dietary intake and biochemical findings, individual clinical stigmata and biochemical status and between clinical stigmata and scores in the test of physical fitness were investigated (Figure 3, Table 12). The results will be discussed later in conjunction with similar data for the Indian troops.

PHYSICAL FINDING	AVERAGE DIFFERENCE BETWEEN MEN WITHOUT AND WITH THE PHYSICAL FINDING, CALCULATED FOR INDIVIDUAL ISLANDS. FIGURES REPRESENT (WITHOUT MINUS WITH)			
	Ascorbic Acid	Thiamine	Riboflavin	Step Test Score
	mg./hr.	*mcg./hr.*	*mcg./hr.*	
Eyes				
Dryness of eyes	+0.02	+3.6	+4	−10
Changes in opacity of sclerr	+0.03	+0.4	+1	0
Changes in opacity of cornea	+0.06	−1.6	−13	−6
Gross conjunctivitis	−0.05	−2.2*	−3*	+5*
Pterygia	+0.14	+1.0	−6	+5
Pinguculae	−0.03	−0.9	−2	+2
Lips and mouth				
Gingivitis	+0.02	+0.3	+2	+5*
Inflammation of dental mnrgin	−0.05	−3.6	0	+4
Swelling of interdental papillne	+0.04	+2.3	−2	+2
Bleeding of gums	+0.06	+1.1	+5	+6
Fair and poor oral hygiene	+0.11	+1.0	+5*	+5*
Skin				
Follicular hyperkeratosis	−0.04	−1.2	+6	−7
Acneform eruption	−0.01	−1.1	−7*	+2

* Analysis of variance shows that the probability is less than 1 in 20 that these differences are due to random variations.

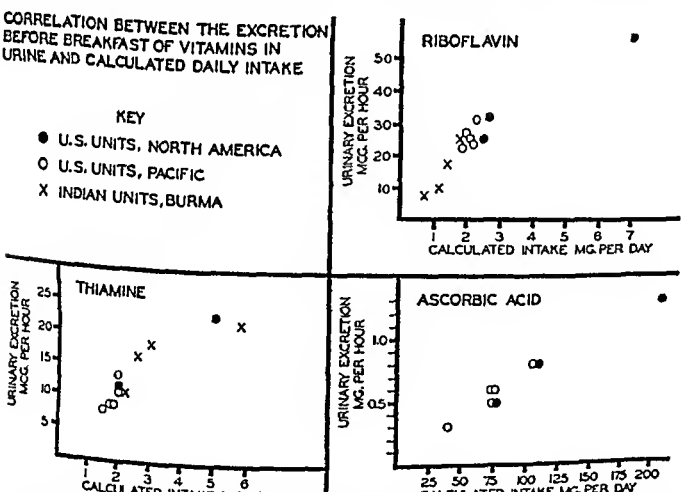


FIG. 3. CORRELATION BETWEEN CALCULATED AVERAGE DAILY INTAKE AND MEASURED EXCRETION OF RIBOFLAVIN, THIAMINE AND ASCORBIC ACID IN SAMPLES OF URINE COLLECTED BEFORE BREAKFAST FROM U. S. TROOPS IN THE PACIFIC, U. S. TROOPS IN NORTH AMERICA AND INDIAN TROOPS IN BURMA

Points for U. S. troops in Pacific and North America of approximately fifty men each. Points for Indian troops of 39, 55, 72 and 140 men. Troops excreting large amounts of mine (93 mcg./hr.) and ascorbic acid (1.4 mg./hr.) were their regular rations.

containing large amounts of ascorbic acid was good. Other places fell between the extremes seen on Guadalcanal and on Guam, and the overall average excretion was slightly below that found in the United States.

I. Diagnoses

As a result of the clinical and biochemical studies, no diagnoses were made among U. S. troops in the Pacific Theater of Operations of the specific deficiency

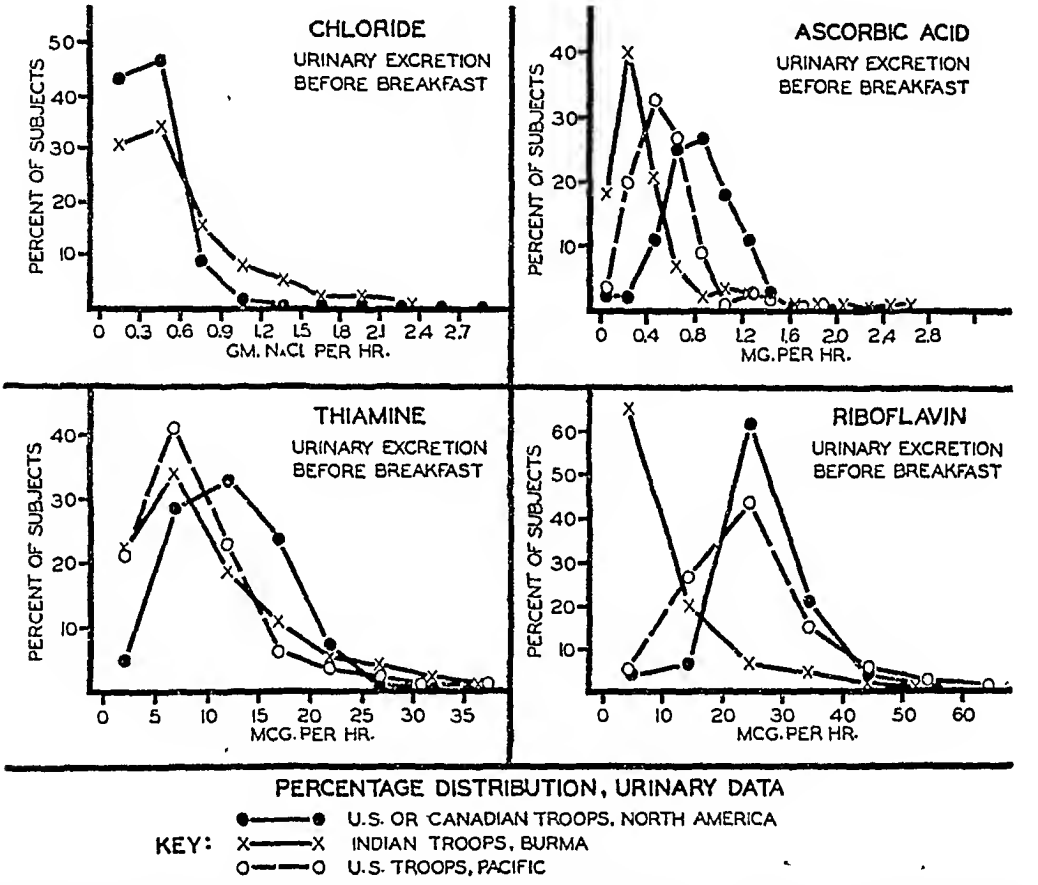


FIG. 2. PERCENTAGE DISTRIBUTION CURVES FOR DATA ON CHLORIDE, ASCORBIC ACID, THIAMINE AND RIBOFLAVIN EXCRETION IN SAMPLES OF URINE COLLECTED BEFORE BREAKFAST FROM U. S. TROOPS IN THE PACIFIC (300 MEN), INDIAN TROOPS IN BURMA (1000 MEN) AND U. S. INFANTRY IN COLORADO (600 MEN)

diseases scurvy, beri-beri, pellagra, xerophthalmia or "hunger edema." Some evidence was found of moderate caloric deficit in groups under stress of combat.

J. Dietary, Biochemical and Clinical Correlations

The relationships between dietary intake and biochemical findings, individual clinical stigmata and biochemical status and between clinical stigmata and scores in the test of physical fitness were investigated (Figure 3, Table 12). The results will be discussed later in conjunction with similar data for the Indian troops.

TABLE 12

Correlations Among Physical Findings, Urinary Excretion of Vitamins and Step Test Scores, U. S. Troops in Pacific

PHYSICAL FINDING	AVERAGE DIFFERENCE BETWEEN MEN WITHOUT AND WITH THE PHYSICAL FINDING, CALCULATED FOR INDIVIDUAL ISLANDS. FIGURES REPRESENT (WITHOUT MINUS WITH)			
	Ascorbic Acid	Thiamine	Riboflavin	Step Test Score
	mg./hr.	*mcg./hr.*	*mcg./hr.*	
Eyes				
Dryness of eyes	+0.02	+3.6	+4	−10
Changes in opacity of sclera	+0.03	+0.4	+1	0
Changes in opacity of cornea	+0.06	−1.6	−13	−6
Gross conjunctivitis	−0.05	−2.2*	−3*	+5*
Pterygia	+0.14	+1.0	−6	+5
Pingueculae	−0.03	−0.9	−2	+2
Lips and mouth				
Gingivitis	+0.02	+0.3	+2	+5*
Inflammation of dental margin	−0.05	−3.6	0	+4
Swelling of interdental papillae	+0.04	+2.3	−2	+2
Bleeding of gums	+0.06	+1.1	+5	+6
Fair and poor oral hygiene	+0.11	+1.0	+5*	+5*
Skin				
Follicular hyperkeratosis	−0.04	−1.2	+6	−7
Acneform eruption	−0.01	−1.1	−7*	+2

* Analysis of varianco shows that tho probability is less than 1 in 20 that these differences aro due to random variations.

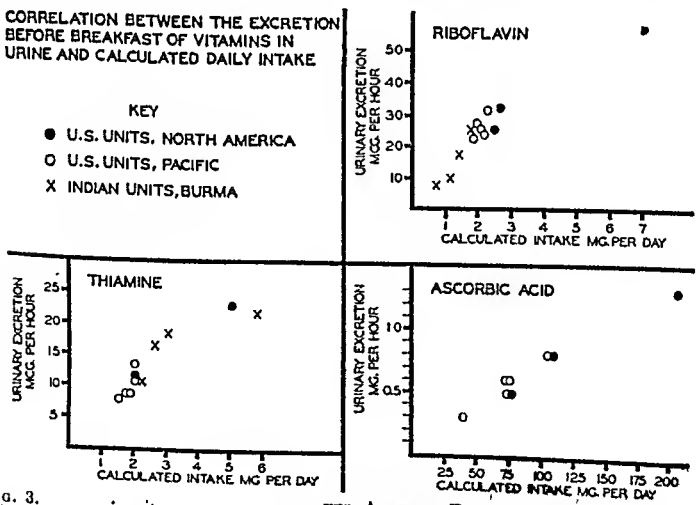


FIG. 3. EXCRE ... TEN AVERAGE DAILY INTAKE AND ... COL ... ANN ASCORBIC ACID IN SAMPLES OF U ... FROM U. S. TROOPS IN U. S. IN NORTH AMERICA AND INDIAN T

Points for U. S. troops in Pacific and North America ... approximately fifty men each. Points for Indian troops ... for ...

SOUTHEAST ASIA COMMAND (INDIA AND BURMA)

A. Troops Surveyed

Place	*Units*	*Date*
Mohand, U.P.	7/10 Gurkha Rifles	23 Jan.–16 Feb. 1945
Monywa and Alon Areas · Burma	1568 Indian Pioneer Co.	1–5 April 1945
	1355 Indian Pioneer Co.	1–5 April 1945
	1318 Indian Pioneer Co.	3–10 April 1945
	151 General Purpose Transport Co.	10–14 April 1945
	11 Operational Research Group	10–14 April 1945
	11 Malaria Forward Treatment Unit	14–18 April 1945
	Hq. 552 Sub-Area	18–21 April 1945
	578 Indian Supply Platoon	18–24 April 1945
	18 Field Bakery Co.	18–26 April 1945
Meiktilla and Thazi Areas	33 Animal Transport Co.	4–7 May 1945
	169 Motor Transport Co.	7–10 May 1945
	41 Animal Transport Co.	10–15 May 1945
Pegu Area	3/9 Jat Regiment	25–28 May 1945
	Japanese Prisoners of War	25–28 May 1945
	69 Anti-malaria unit	3–5 June 1945
	2/1 Punjab Regiment	5–7 June 1945
Rangoon and Mingladon Area	Probyns Horse	28 May–3 June 1945
	Deccan Horse	
	33 Corps Defense Co.	8–10 June 1945
	1st 1 Light Anti Aircraft Regt.	10–13 June 1945
	81 Workshop Co. 1 E.M.E.	13–17 June 1945
	6 Bombay Engineers	17–22 June 1945
	232 Bomb Demolition Co.	22–24 June 1945

In all 23 different units and formations were studied, including infantry, armored corps, artillery, engineers, medical, motor or animal transport, pioneers and Japanese prisoners. Among the Indian troops the main racial groups included Gurkhas, Punjabis, Sikhs, Rajputs, Mahrattas, Bengalis, Jats, Pathans, Waziri, Dogras and Bihari. The main religions represented were Hindus, Mohammedans and some Christians. High and low castes were represented. The average age was 25 years; the average height, 5 feet 6 inches; the average weight, 126 pounds; and the average length of time in service in forward areas 21 months (for comparison with U. S. troops see Table 2).

B. Rations and Nutrient Intake

The Field Service Ration Scale (Indian Troops) was used in forward areas. This consists of perishable and non-perishable foods in large variety. Packaged combat rations included the Indian Eight Man Compo Ration, consisting of tinned and packaged food for eight men for one day and the Indian Type Light Scale Ration, providing food for two men for one day. Supplements included chickens, mangoes and bananas which were obtained on occasion from the Burmese. Two fairly reliable and typical unit food issues are shown in Table 13 contrasting the raw food-stuffs available to a rice-eating Indian soldier with those available to an atta-eating Indian soldier. (Atta is a coarse whole wheat flour which is usually eaten in the form of chapatties, a kind of flap jack.) The

items on the ration scale which were not fully utilized included meat, which was seldom available or canned milk in lieu of meat; jam, cheese, atta or rice, fresh vegetables and fruits during seasonal scarcities, and dehydrated vegetables. Dal (lentils), sugar, ghi (clarified butter) and fish were nearly always in full supply.

Several types of processed foods were highly acceptable. Canned milk, both sweetened condensed and unsweetened evaporated were avidly drunk from the can by the individual Indian soldier. Canned vegetables, especially leafy vegetables such as spinach, were well liked except when issued too frequently. Canned fruits were popular. Canned salmon and sardines were acceptable except when issued too frequently, but canned herring was never popular. Jam, canned

TABLE 13

Comparison of Raw Food Issued to an Atta (Wheat) Eating Indian Unit and to a Rice Eating Indian Unit

Food allowed and actually drawn for one soldier for one day

COMMODITY	DAILY ALLOWANCE	AMOUNT ACTUALLY DRAWN	
		Atta Eating Unit	Rice Eating Unit
	gm.	*gm.*	*gm.*
Atta (Coarse wheat flour)	680, combined	425	220
Rice		115	435
Sugar	80	85	80
Jam	11	7	0
Milk (Canned)	85	95	160
Cheese	30	40	0
Meat	115	0	0
Fish	45	55	45
Dal (Legumes)	100	90	85
Potatoes	115	70	140
Other vegetables	285	225	130
Fruit	100	70	50
Ghi (Clarified butter)	75	80	70

cheese, biscuits and rock salt were not very popular in the forms issued. Because of difficulty of supply in Burma alcoholic beverages consisted of an occasional issue of rum together with small amounts of toddy wine obtained from Burmese villages.

Food Prejudices. The Indian army, which draws its recruits from all India, contains Mohammedans who will only eat "halal" meat (slaughtered by cutting of the great vessels in the neck) and who abhor pork, Hindus who abhor beef and the meat of female animals, and who slaughter by "jhatka" (decapitation) as well as Jats (Hindus) and other strict vegetarians together with a small percentage of Christians. Generally speaking, the Indian soldier was suspicious of any meat which had been processed, such as dehydrated goat's meat. He was even suspicious of properly certified "jhatka" or "halal" dressed carcass meat and some troops would only eat meat delivered on the hoof. Consequently the meat

intake, especially in the so-called better regiments was negligible. However, it has been observed that some lower castes of Madrassis, Gurkhas and Sikhs (mainly working in rear areas) ate imported meat products without any compunction. This was done quite openly. In forward areas it has been reported, and a few instances were observed, where Indian soldiers of all castes ate "bully" and other prohibited foods. Such food was usually eaten surreptitiously. On the other hand a vegetarian Jat has been observed to throw away a can of evaporated milk, because it was "contaminated" by being opened with a can opener which had just been used on a can of salmon.

Unlike the Royal Indian Navy and the Royal Indian Air Force which insists on mixed messing for all castes and religions, the 14th Army provided separate kitchens and separate types of rations.

The Indian Soldier's Meals. The day usually started around 5:00 A.M. with sweet milky tea and in some units chapatties, parata (wheat and oil) or shakapura (whole grain) biscuits. At 10:30 or 11:30 A.M. the soldier had chapatties or rice with a vegetable curry. At 2:30 P.M. tea was again brewed and at about 5:30 P.M. he had his big meal, of chapatties or rice, with a vegetable curry to which fish, eggs or meat were added when they were available. Canned, fresh or dried fruit was usually eaten with this meal.

During activity in the field, such as patrols, the individual soldier or small groups of soldiers frequently prepared their own food. Often very little besides cold chappatties or rice was taken along on patrols. The Indian type of light scale ration and the composite ration were also used but often individual items such as biscuits were discarded and not carried in the pack. Tank crews experienced considerable difficulty in preparing adequate meals from the Field Service Ration Scale.

Cooking and Cooks. Usually cooking was done over wood fires built in shallow trenches. Cooking equipment was simple and consisted of large iron stewpots and a flat iron plate for cooking chapatties. Generally speaking the Indian cooks were not well trained and had little imagination or initiative. They made little or no attempt to prepare palatable dishes from processed foodstuffs, and even traditional Indian dishes such as palaws (a kind of stew) hardly ever replaced the invariable curries which were nearly always cooked for hours at high temperatures.

Nutrient Intake. Accurate estimates of nutrient intake were prevented in many places by several difficulties, including inaccurate scales for issuing rations in rear areas, rough and ready issuing of rations in forward areas without the use of scales, inadequate data on wastage in preparation, losses in cooking and plate waste, and the language handicap which led to inaccuracies in histories elicited from individual soldiers. A fairly reliable and typical set of data is shown in Table 14 contrasting the nutrients in the raw food issued per day to a rice-eating and to an atta-eating Indian soldier. By ordinary North American standards, total calories, total protein, thiamine and niacin were all high, but animal protein, vitamin A, riboflavin and ascorbic acid were all low. The atta eaters' food issue contained much more thiamine than the rice eaters'.

A few units such as the pioneers and engineers paid particular attention to salt intake. In these units drinking water was salinated or special care was taken to see that quantities of salt were mixed with atta before chapatties were made. Generally speaking the troops took salt only as a condiment added to their food. Tank crews were supposed to take 5 grams of salt extra for each two hours they were "closed down." No estimates of water intake were possible except in the case of tank crews who used approximately three gallons per day for drinking and cooking.

C. Medical History

Because of language difficulties detailed clinical histories were not taken from each man. Spontaneous complaints, however, were noted and when lesions were present leading questions were often asked. Unit histories were obtained from

TABLE 14

Calculated Nutritional Value of Raw Food Drawn by an Atta (Wheat) Eating Indian Unit and by a Rice Eating Indian Unit

Important nutrients available to one man in one day

NUTRIENT	ATTA (WHEAT) EATING UNIT	RICE EATING UNIT
Total Calories	3,850	3,940
Protein, total, gm	126	110
Protein, animal, gm	26	23
Fat, gm	80	82
Carbohydrate, gm	615	705
Vitamin A, I.U.	2,080	1,390
Thiamine, mg	4.0	2.5
Riboflavin, mg	1.1	1.1
Niacin mg	23	20
Ascorbic Acid, mg	40*	50*

* Highly variable owing to variety of sources and methods of cooking foods.

officers. In those units where environmental stress had existed many of the ment complained of illness. The commonest complaints were referable to the gastrointestinal tract, e.g., stomach ache, anorexia, diarrhea and cramps; and to the cardio-respiratory system, with collapse, palpitation, pain in the chest and fatigue. Some complained of night blindness and others of muscular cramps. In two units, one a tank regiment and the other a mule transport unit the officers reported that men had been evacuated with a diagnosis of "heat stroke." Officers in all units reported that malarial casualties had been rare since the introduction of atabrine.

D. Physical Examination

On examination the majority of Indians were fit and healthy looking. Generally speaking they were very lean, and while their musculature and general development were inferior by British and North American standards their muscle

TABLE 16

Average Values, Blood and Urine Data, Indian Soldiers, British 14th Army

UNIT	NUMBER OF MEN	HEMOGLOBIN	SERUM PROTEIN	SERUM CHLORIDE	URINARY CHLORIDE (FASTING)	SERUM ASCORBIC ACID	URINARY ASCORBIC ACID (FASTING)	URINARY THIAMINE (FASTING)	URINARY RIBOFLAVIN (FASTING)	URINARY N¹-METHYLNICOTINAMIDE (FASTING)
		gm./100 ml.	*gm./100 ml.*	*meq./liter*	*gm. NaCl/hr.*	*mg./100 ml.*	*mg./hr.*	*mcg./hr.*	*mcg./hr.*	*mg./hr*
3/9 Jat	35	12.6	5.9	98	0.3	0.1	0.4	18	5	0.8
2/1 Punjab	60	14.1	6.3	99	0.3	0.2	0.3	11	3	0.2
7/10 Gurkha Rifles	140	14.4	5.3	104	0.7	0.2	0.5	15	6	0.6
33 Corps Defence Co.	70	13.9	5.8	98	0.5	0.1	0.6	15	6	0.4
Probyns Horse I.A.C.	42	15.2	5.9	98	0.4	0.2	0.4	8	5	0.4
Deccan Horse I.A.C.	50	15.1	5.9	97	0.3	0.2	0.3	7	4	0.2
6 Bombay Engineers I.E.	50	15.0	6.1	103	1.2	0.2	0.6	10	7	0.5
354 Bomb Disposal Co. I.E.	49	14.3	6.1	101	0.6			11	7	0.3
Light Anti-aircraft Battery I.A.	75	14.2	5.8	100	0.4	0.1	0.6	12	6	0.4
81 Mobile Workshop I.E.M.E.	48	14.9	5.9	99	0.5	0.1	0.5	10	6	0.4
151 Gen. Purpose (Motor) Tpt. Co.	35	13.8	5.4	108	0.7	0.1	0.4	17	10	0.6
169 G.P. (Motor) T. Co. R.I.A.S.C.	35	14.9	6.1	102	0.5	0.2	0.2	8	38	0.3
33A. (Mule) T. Co. R.I.A. S.C.	34	13.1	5.6	99	0.2	0.1	0.3	8	32	0.4
41A. (Mule) T. Co. R.I.A. S.C.	70	13.1	5.7	99	0.2	0.1	0.2	8	14	0.4
69 Anti Malaria Unit I.A.M.C.	25	14.4	6.2	102	0.4	0.3	0.8	17	5	0.2
11 M.F.T.U. I.A.M.C.	21	13.0	5.7	101	0.5	0.1	0.3	12	21	0.9
1568 Indian Pioneer Co. I.P.C.	35	15.8	5.5	107	0.8	0.1	0.3	5	22	0.8
1318 Indian Pioneer Co. I.P.C.	35	16.3	5.5	108	0.8	0.1	0.3	5	13	0.6
1355 Indian Pioneer Co. I.P.C.	34	15.9	5.7	104	0.8	0.1	0.3	5	16	0.8
578 I. Supply Co. R.I.A. S.C.	33	14.3	5.7	99	0.4	0.4	0.7	20	6	0.1
18 Field Bakery R.I.A.S.C.	15	15.0	5.8	99	0.4	0.3	0.5	16	7	1.0
Clerks H.Q. 552 Sub Area R.I.A.S.C.	10	14.1	6.1	100	0.5	0.2	0.8	20	6	1.1
Orderlies 11 O.P.S. Research Group	18	15.8	5.8	97	0.4	0.3	0.3	14	6	0.8
All Indian Soldiers	1,019	14.4	5.8	101	0.5	0.17	0.4	12	10	0.5
Canadian and U. S. Infantry, North America		15.8	6.5	104	0.7	0.7	0.8	12	26	0.3

Among men who had been two years in a forward area, the average hemoglobin level was lower by 1.4 gm. per 100 ml. (Table 18) than among men newly arrived. Part of this decrease may be ascribed to malaria and other parasitic diseases, but part of it may also have been caused by a low intake of animal protein and other nutrients while in service. In confirmation of this idea, the lowest average hemoglobin level in any racial or religious group studied was among Jat soldiers who are

TABLE 17

Comparison of Average Measurements on Blood and Urine of Atta (Wheat) Eating and Rice Eating Indian Soldiers

SUBSTANCE MEASURED	ATTA (WHEAT) EATERS	RICE EATER
Hemoglobin, gm./100 ml.	14.2	15.5
Serum protein, gm./100 ml.	5.7	5.7
Serum chloride, meq./liter	100	105
Serum ascorbic acid, mg./100 ml.	0.1	0.1
Urinary chloride, gm. NaCl/hr.	0.4	0.7
Urinary ascorbic acid, mg./hr.	0.4	0.3
Urinary thiamine, meg./hr.	15	6
Urinary riboflavin, meg./hr.	5	15
Urinary N^1-methylnicotinamide, mg./hr.	0.5	0.4

TABLE 18

Biochemical Status of Indian Soldiers, British 14th Army, in Relation to Length of Service in Forward Areas

SUBSTANCE MEASURED	TIME IN FORWARD AREAS (MONTHS)		
	0 to 6 (171 men)	7 to 12 (158 men)	13 to 24 (160 men)
Hemoglobin, gm./100 ml.	15.0	14.2	13.6
Serum protein, gm./100 ml.	5.8	5.7	5.7
Serum chloride, meq./l.	103	99	101
Urinary chloride, gm. NaCl/hr. (Fasting)	0.8	0.4	0.4
Serum ascorbic acid, mg./100 ml. (Fasting)	0.2	0.2	0.1
Urinary ascorbic acid, mg./hr. (Fasting)	0.5	0.5	0.4
Urinary thiamine, meg./hr. (Fasting)	10	12	14
Urinary riboflavin, meg./hr. (Fasting)	11	6	12
Urinary N^1-methylnicotinamide, mg./hr. (Fasting)	0.3	0.4	0.5

strict vegetarians. Macrocytic anemias have been reported to be common among civilian vegetarians (Taylor and Chuttani, 1945). Madrassi and other rice eaters had higher hemoglobin levels that atta eating soldiers. This fact possibly supports a current hypothesis that atta contains substances interfering with hematopoiesis.

Serum Protein. Thirty-nine per cent of subjects had serum protein levels above 6.0 gm. per 100 ml. and fifteen per cent had levels less than 5.3 gm. per 100 ml. One man had edema of the legs and a protein concentration of 4.3 gm. per

the 80 scored by a very good platoon of infantry in Canada (Kark, et al. 1945), the 81 scored by the subjects from the U. S. 38th Infantry Division on Luzon, and the 85 scored by a well trained U. S. infantry battalion in Colorado. Physical examination revealed few positive physical findings and those were not severe. Biochemical studies demonstrated serum protein levels and urinary excretion of riboflavin considerably lower than those encountered in North American troops (Table 19), while serum and urinary ascorbic acid and average hemoglobin levels were somewhat lower.

We conclude that excellent physical fitness and tactical efficiency are compatible with what by ordinary North American standards are low levels of several important constituents of the body notably riboflavin, serum protein and ascorbic acid.

H. Diagnoses

No full blown cases of the specific nutritional diseases scurvy, beri-beri or pellagra were seen in Indian troops. Nevertheless, in individual cases stigmata were seen which by orthodox interpretation are often attributed to nutritional deficiencies, and similarly very low levels were found of important constituents of the body. The two findings were not necessarily in the same individuals. On the basis of history, physical examination and laboratory findings diagnoses were made of anemia, chronic caloric deficiency and salt depletion. Tentative diagnoses were made of ariboflavinosis associated with tissue changes.

IV. GENERALIZATIONS BASED ON COMPARISON OF TROOPS IN NORTH AMERICA, THE PACIFIC AND BURMA

A. Effects of Stress, and "Tropical Deterioration"

The effects of the stress of combat on well-fed troops among whom tropical diseases were well controlled may be seen by comparing U. S. troops in rear areas of the Pacific with those recently in combat. Iwo Jima had been taken twelve weeks before the survey team arrived, and battles on Okinawa and Luzon were still in progress. There had never been any fighting on the island of Hawaii, and at the time of survey Guadalcanal had been secure for two years and Guam for six months.

Symptoms referable to the skin, gastrointestinal tract and neuromuscular systems tended to be commoner in the groups under stress of combat (Table 7). Positive physical findings were also commoner, especially conjunctivitis, gingivitis, poor oral hygiene, folliculitis, miliaria, fungus infections and epidermophytosis (Table 8). Weight was lowest on Iwo Jima and Luzon (Table 9). On the other hand, physical fitness was actually better in those exposed to stress (Table 10) and biochemical status was not strikingly different in the two groups (Table 11).

Although there is no quantitative way of measuring morale, one can usually determine from conversations with commissioned and non-commissioned officers and by personal observation of the troops whether it is good or bad. In the Pacific morale was good where men had a job to do of obvious immediate

importance, and in general was better the further forward they were. On Hawaii and Guadalcanal, morale was poor; on Guam, fair; and on Iwo Jima and in the 38th Infantry Division on Luzon after fourteen consecutive weeks in the front line, it was excellent.

These U. S. troops recently in combat were adequately fed men without serious disease who showed some wear and tear but could still carry on well and do their job efficiently. A different picture was seen in one Indian unit which deteriorated badly as a result of prolonged and severe stress accentuated by an inadequate diet.

Two Indian units, attached to the same infantry brigade, worked between air landed supply dumps and forward areas and had served in Burma without relief for a continuous period of 30 months. Marked differences in physical fitness, health and biochemistry were demonstrated although both units had been on active service in Burma for similar periods of time, both had received the same rations and at least from the Army's point of view both had been engaged in the same work in the same country under exactly similar climatic conditions. One unit used motor vehicles to transport materiel the other packed supplies on mules and had to march to their objectives.

Analysis of the stresses which affected both units showed that the muleteers (41 Animal, Mule, Transport Co., RIASC) expended over 4500 Cals. daily in marching, in taking care of the mules and in constructing defenses. They had little rest, since sleep in the field was often disturbed by the enemy. During the day they were exposed to sun, wind and rain. They subsisted on a standard Army ration which was often reduced by ⅓ or ½ because of the tactical situation. They did not supplement their rations to any appreciable extent because of religious scruples and lack of opportunity. Being in contact with the enemy they seldom used mosquito nets and with excessive sweating and high water requirements they were accustomed to quench their thirst with unsterilized water when watering their mules. Skin infections were common because of contact with their animals, thorn scratches, insect bites and lack of opportunity to bathe. Malaria and diarrhea rates were high.

The motor transport company (169 General Purpose Motor Transport Co., RIASC) on the other hand expended only 3500 Cals. daily in driving vehicles for long hours over poor roads. Rest was possible during loading and unloading and they slept fairly comfortably in the back of their trucks. They usually harbored at night with large formations and consequently did not have to construct defenses; nor was their sleep often disturbed by enemy activity. During the day they were protected from sun, wind and rain. They and the muleteers had exactly similar ration issues, but the motor unit frequently supplemented rations with imported British and U. S. Army processed meats since religious food taboos were not strict. Their water requirements were not high and boiled tea was their common drink. They could erect mosquito nets easily inside their vehicles. Malaria and diarrhea rates were not so high as in the muleteers. Skin infection was negligible.

As judged by clinical examination and biochemical studies the men of the motor

transport company were adequately nourished, and although tired, were physically fit and well enough to carry on their duties efficiently. The men of the animal transport company, on the other hand, were thin, haggard, fatigued and at the end of their tether. Their physical fitness, judged both by the pack test, by our own observations and by the opinions of their officers, was at a low ebb and they could no longer carry out their operational duties efficiently. Over half the men complained spontaneously of vague symptoms including palpitation, fatigue, collapse on the march, muscular and abdominal cramps, gastrointestinal disturbances and visual defects. A comparison of the biochemical findings is given in Table 19, which demonstrates that blood and urinary levels of the mule transport unit were well below those of the motor transport unit.

On the basis of clinical examination and biochemical findings, diagnoses were made in the mule transport unit of chronic caloric deficiency, chronic anemia, salt depletion and mild vitamin B complex deficiency.

The concept of a specific deleterious effect of climate on white settlers in the tropics has been elaborated by many writers (e. g. Castellani, 1938; Price, 1940; Reed, 1942) who describe the syndrome of "tropical deterioration," "tropical neurasthenia" or "cacophoria tropicalis." Most descriptions of the syndrome among white settlers have been based on observations of a qualitative nature on individuals whose mental or physical health was not at a high peak. There is little definite knowledge of the etiology of the syndrome or of the relative importance in it of neuropsychiatric and physiological factors. The tacit implication is made by most authors that the syndrome is common, and that it will occur in a high percentage of white people who make their homes in the tropics.

As seen in U. S. troops (Editorial, Bulletin U. S. Army Medical Dept., 1944) it includes: poor physical condition; chronic fatigue states; sometimes chronic diseases; deterioration in character, memory, initiative and responsibility, and a variety of psychosomatic complaints. Lee (1940, 1944, 1945) has concluded from his studies on civilians and troops in Australia and New Guinea that tropical deterioration is not a specific entity to be differentiated from deterioration seen elsewhere. With his conclusions we are in general agreement and can contribute to the question in two ways.

First, white troops were fighting winning battles after continuous presence for as much as three years in severe tropical environments. They received good medical care, led an active life and maintained satisfactory health. Nevertheless, psychological changes for the worse were present in some rear areas where men were isolated for no reason satisfactory to them, and yet these men were facing less danger, discomfort and disease than those further forward in whom morale and performance were good in spite of severe climatic stresses.

Second, under certain well recognized types of stress, men will react and deteriorate similarly in tropical and in temperate or cold environments. The survivors of the U. S. 38th Infantry Division on Luzon showed weight loss and other effects of a long campaign. Nevertheless, they had good efficiency, high morale and a generally good nutritional state. In the mule transport company in Burma we had a group showing deterioration along with diseases, positive

physical changes and poor biochemical status. They showed the same sort of deterioration as units in temperate climates (Canadian Army Report, NRC, Canada, 1943) or subarctic climates when exposed to stresses beyond their breaking point (Kark, Johnson and Lewis, 1945).

We conclude that the factors leading to deterioration in military personnel in the tropics are in some cases the same as they are in temperate or cold environments. We have seen little evidence of a specific effect of the tropics except for skin diseases, especially miliaria and fungus injections. Neither have we seen cases of deterioration which could be diagnosed as purely tropical or climatic in origin. When deterioration does occur, as in the mule company, it is our impression that it may be more disabling than elsewhere because of the natural environmental handicaps which exist in warm, humid climates.

B. Interrelations Among Dietary Intake, Biochemical Measurements, Physical Efficiency and Clinical Findings

In most nutrition surveys of general populations information is collected in several ways. Dietary intake is estimated by laboratory analysis of meals, by calculation from dietary histories, or by calculation from data on food supplies. Clinical assessments are made from histories, clinical examinations and special techniques such as slit lamp examination and x-ray studies of bones and bowels. Biochemical analyses are usually carried out on blood and urine. Fitness, efficiency and work output are rarely estimated in any quantitative manner. In the past implicit or explicit assumptions have frequently been made first, that there are close correlations among the different types of data collected by the methods outlined; and second, that it is possible to set minimal values below which there is ill health (Adamson et al., 1945). Our present observations allow several conclusions to be drawn on these points.

The first general conclusion is that within a "normal population," i.e., one that is able to work efficiently and is not ill enough to be hospitalized, there is reasonable correlation between the average intake of various substances for a period of months and their average concentration in the blood or excretion in the urine. This may be seen by comparing in both the U. S. and Indian data on protein intake and plasma protein, ascorbic acid intake and serum and urine ascorbic acid, and thiamine and riboflavin intakes with the urinary excretions of these vitamins (Figs. 1, 2 and 3; Tables 6 and 13). These findings are consistent with other reports and would be anticipated on a priori grounds (Johnson, Henderson, Robinson and Consolazio, 1945). It should be emphasized that this generalization holds for average values for large groups, and that individual measurements may show a fairly wide range.

Another general conclusion is that within a "normal population" as defined in the preceding paragraph, the measurements made in the present surveys showed few correlations among biochemical values, physical fitness and clinical findings.

The relationships between individual clinical stigmata and biochemical status and between clinical stigmata and step test scores were investigated in U. S. troops. In the first place the average difference in biochemical values and step

test scores between men with a particular stigma and men without the stigma were determined for each island. These intra-island differences were then averaged, and the harmonic means of intra-island "clinically normal" and "clinically abnormal" men were used as weighting factors. The magnitudes of these intra-island differences were tested for significance by comparing them with pooled intra-island variances. Only a few statistically significant correlations were found (Table 12). Slightly low step test scores correlated with gross conjunctivitis, gingivitis, and poor oral hygiene. Slightly low riboflavin values were

TABLE 20

Average Biochemical Values for Indian Soldiers with Positive Physical Findings Compared with Averages for All Indian Troops

(Compare Table 12 for U. S. troops)

PHYSICAL FINDING	NUMBER OF CASES	SERUM ASCORBIC ACID	URINARY ASCORBIC ACID	URINARY THIAMINE	URINARY RIBOFLAVIN
		mg./100 ml.	*mg./hr.*	*mcg./hr.*	*mcg./hr.*
Eyes					
Dryness	13	0.14	0.33	8.0	13.8
Change in Opacity Sclera	100	0.18	0.35	10.0	12.7
Change in Opacity Cornea	100	0.16	0.30	8.6	10.1
Gross Conjunctivitis	20	0.19	0.44	11.3	8.9
Corneal Vascularization	100	0.16	0.34	10.3	10.2
Lips, Mouth					
Cheilosis	59	0.17	0.37	11.6	11.0
Angular Fissure	62	0.18	0.37	8.9	13.5
Poor oral hygiene	100	0.17	0.39	10.6	15.5*
Good oral hygiene	100	0.19	0.42	11.1	10.4
Skin					
Follicular hyperkeratosis	49	0.13*	0.38	10.8	15.3
Acneform eruption	29	0.23*	0.45	11.5	8.0
Seborrheic dermatitis	5	0.14	0.35	9.5	6.6
1,029 Indian Troops		0.17	0.4	12	10

* Analysis of variance shows that the probability is less than 1 in 20 that these averages differ by chance variation from the average of men not having the physical finding.

correlated with poor oral hygiene, and a statistically significant correlation existed between increased excretion and gross conjunctivitis and acneiform eruption. Also, a slightly increased excretion of thiamine was correlated with gross conjunctivitis.

The relationship between individual clinical stigmata and some of the biochemical measurements in Indian troops is shown in Table 20. It will be recalled that for U. S. troops in the Pacific, statistically significant correlations were found between (a) increased excretion of thiamine and gross conjunctivitis, (b) decreased excretion of riboflavin and poor oral hygiene and (c) increased

excretion of riboflavin and both gross conjunctivitis and acneiform eruption (Table 12). Among the Indian troops none of these correlations was found (Table 20). In fact, poor oral hygiene was associated with the highest levels of excretion of riboflavin found in Indian troops (15.5 mcg. per hour) which were still much lower than the lowest average figures found in U. S. troops (21 mcg. per hour). Two correlations among Indian troops were, slightly decreased serum ascorbic acid and follicular hyperkeratosis, and, slightly increased serum ascorbic acid and acneiform eruption. The proliferative eye lesions described in the section on physical examination were not clearly associated with nutritional factors and we can advance no satisfactory hypothesis on their etiology.

The few correlations established were between small average differences, their physiological interpretation was not apparent and they could not be used for diagnostic purposes in individual cases. A different set of results might be expected in a population suffering from florid nutritional disease. Lack of correlation between biochemical and clinical findings has been reported by Milam and Anderson (1944) in North Carolina, by Riggs et al. (1943) in Canada and by Youmans et al. (1942, 1943) in Tennessee, and some of the many possible contributing causes for this situation have been discussed by Sinclair (1944) and by Dann and Darby (1945). In a well controlled laboratory experiment, imposition of a deficient diet is followed in order by chemical unsaturation of the tissues, by impairment of function without histological changes and finally by definite pathological changes in the tissues. In natural environments the interpretation of changes is difficult. A subject previously unsaturated may have had recent access to nutrients enough to raise his tissue concentration without restoring function or reversing pathological changes. Again, disturbance of nutrition is only one of many possible causes of functional impairment. Finally, a given pathological change, such as cheilosis may result from one or many processes other than nutritional deficiency (Machella, 1942; Machella and McDonald, 1943). Pett (1945) has emphasized another phase of the lack of correlation among chemistry, function and pathology. Many characteristics of a population can be expressed in distribution curves. An individual subject provides a single point on each curve but there is no valid reason to expect that measurements on him will always fall in the same portion of every curve. For instance there should be no occasion for surprise that a man should be classified as having a high degree of fitness and yet as having a low serum ascorbic acid and at the same time normal optic discs. Since it is excessively uncommon for a single type of observation to be diagnostic for any specific disease, extreme caution should be used in interpreting data on the lower end of distribution curves. So far as nutrition is concerned, it may be that a whole population is so well fed that even those whose measurements are on the lower ends of the distribution curve are by any reasonable standard not at all deficient, and this is the exact interpretation we place on the data for U. S. troops in the Pacific. In contrast, some of the distribution curves for the Indian troops had lower values than those for U. S. troops and there were in Burma actual cases of ill health associated with positive clinical findings and poor biochemical states.

C. Relation of Present Surveys to Troop Feeding

During the war several ration trials in North America gave systematic quantitative information on food habits, on likes and dislikes of U. S. and Canadian soldiers and on the effects of several types of rations on men working in cold and in temperate environments. A logical fulfillment of the implications of these ration trials was the conduct of similar types of study in theaters of war. This was essential not only to validate or invalidate the conclusions from the tests themselves but to assist in establishing a quantitative basis of fact in matters of army nutrition in the field.

Observations on troop feeding in North America, Asia and the Pacific have led to certain general conclusions (Canadian Army Reports, NRC Canada, 1943, 1944; Armored Medical Research Laboratory Report 1944; Indian Army Reports, NRC Canada, 1945). In providing rations for soldiers at least three considerations are of prime importance. First, a considerable variety of food items should be issued. Second, the food items should be much the same as soldiers are accustomed to in ordinary life, but emphasis should be placed on acceptable foods of high biological value. Third, caloric deficits must be avoided. From the standpoint of military efficiency, caloric deficiency was an important problem during the war; vitamin deficiencies, relatively unimportant.

For insuring adequate nutrition several steps are important. Before they are procured for general issue, packaged and non-packaged rations alike should be adequately tested under field conditions for palatability and acceptability and at the same time for their effect on troops. Whatever items are procured have to be properly protected against deterioration and handling throughout the whole line of supply to forward areas. Rations should be used as designed if nutritional disturbances are to be avoided; and if food preparation is not satisfactory even the best designed ration may fail to supply adequate nutrition because of poor acceptability.

As an example of successful troop feeding U. S. troops in the Pacific may be cited. In our opinion their generally good nutrition was to a considerable extent helped by ample supplies of a wide variety of foods including frozen meat, frozen eggs, butter, fresh bread, vegetables, fruit and in some places ice cream. The one U. S. unit we studied that was subsisting exclusively on packaged foods remained fit while receiving a well planned ration in adequate supply.

As an example of unsuccessful troop feeding the mule transport company in Burma may be cited. Because of supply difficulties their rations were inadequate in calories to support the physical work they had to do. In addition some items of high biological values were not palatable, particularly dehydrated male goat meat. Food preparation was unsatisfactory, the cooks being untrained and equipment primitive.

D. Nutritional Requirements in Hot Climates

Nutritional deficiency diseases and poor nutrition are common in the tropics. This situation is contributed to by at least three important factors (Van Veen, 1942). First, population density is high. Second, cheap staple foods, mainly

cereals, tend to be limited in variety in any one region and to be unbalanced in important respects. Finally, disease rates are high. Among the best studies on diet and health in the tropics are McCarrison's (1936). His main conclusions that typical regional, racial and religious diets in India are very different in their ability to promote health have been substantiated by such other workers as Aykroyd (1940). Sikhs have the best civilian diet and Madrassis the worst. The Sikh diet provides an abundance of important nutrients and consists of atta (coarse wheat flour), milk and milk products such as butter, curds and buttermilk, dhal (legumes), vegetables, fruit and meat. When McCarrison fed typical Indian diets to rats, growth and health were best on that of the Sikhs. Of all the castes and races studied by us, only the Sikhs had plasma protein levels in the same range as those of North American troops.

Animal experimentation has led to no general agreement on specific effects of moist heat on nutritional requirements. Mills (1945) has summarized claims that thiamine and choline requirements for rats are increased in moist heat. However, these claims for thiamine are not supported by Sarett and Perlzweig (1943), by Kline, Friedman and Nelson (1945) or by Edison, Silber and Tennent (1945). Most observers agree that the caloric requirements of the rat are less in hot than in temperate climates.

There is much less certain knowledge on human nutritional requirements for life in the tropics than on requirements elsewhere (Van Veen, 1942). The present data from the Pacific and Burma provide information on healthy adult male populations. U. S. troops were adequately fed when their daily nutrient intake included 100 gm. of protein, two-thirds of it animal; 0.7 gm. of calcium; 20 mg. of iron; 5000 IU of vitamin A; 1.8 mg. of thiamine; 2.0 mg. of riboflavin; 22 mg. of niacin; and 75 mg. of ascorbic acid. These figures are in no sense to be construed as recommended allowances. Indian troops in Burma were doing an efficient job in combat, construction and supply while receiving a ration which contained approximately 100 gm. protein, one-fourth of it animal; 2000 IU of vitamin A; 2.5 mg. of thiamine; 1.1 mg. of riboflavin; 20 mg. of niacin; and 40 mg. of ascorbic acid. It is true that on the whole their biochemical status was lower than that of U. S. troops in the Pacific but in such units as the Gurkhas, fitness and health were very good. The data in the present paragraph should not be used to set up recommended allowances. We can give no support to the proponents of high vitamin intakes in the tropics when a healthy adult population is in question. It was our impression that morale, fitness and health of U. S. troops were not affected either adversely or beneficially by sporadic or regular use of vitamin pills. Neither can we support the proponents of a diminished protein intake in the tropics. The arguments for and against this have been discussed by Lusk (1931), by Leitch (1930) by Nicholls (1938) and by Pitts et al. (1944). U. S. troops voluntarily ate 100 or more grams of protein per day and adapted well to the heat. The Indians, with a lower intake of animal protein had associated low levels of hemoglobin and serum protein. Our observations on caloric intake are consistent with, but not conclusive for, the idea that caloric requirements may be less in tropical than temperate regions (Eijkman, 1924;

Martin, 1930). U. S. troops in the Pacific were eating about 400 Cals. per day less than U. S. troops in training camps in the U. S. A. However, without an accurate estimate of daily caloric expenditure in work this fact cannot be interpreted with certainty. To the best of our knowledge no systematic observation has been made on the energy expenditure for a given type of exertion in high, moderate and low temperatures.

SUMMARY

1. During early 1945, surveys on the health of troops in the tropics were made by two separate teams using almost identical methods. The Canadian unit operated in India and Burma where it studied Indian soldiers exclusively. The U. S. unit operated in the Central, South, Southwest and Western Pacific where it studied U. S. troops both white and colored. Both teams collected systematic information on feeding policies and practice, on the diet of individual soldiers and groups of soldiers, on health as determined by medical histories and physical examinations, and on physical fitness. Samples of the urine and blood of each subject were analyzed in specially constructed field laboratories.

2. Statistical analysis demonstrated that for survey purposes systematic observations on relatively small samples of about fifty men chosen by an accurate quota system gave a statistically satisfactory picture of whole organizations or garrisons.

3. The results of the present surveys could be interpreted by comparing them with data collected in two large scale ration trials conducted under rigidly controlled field conditions during 1944 in North America. The observations in the ration trials were made by the same methods used in the present surveys, and two members of each survey team had participated in both of the North American trials.

4. In the Pacific the U. S. team examined garrison troops on Hawaii, Guadalcanal, Guam and Iwo Jima, and combat casualties from Okinawa. Subjects from the 38th Infantry Division on Luzon came from a regiment that had been in combat with the enemy continuously for 4½ months. The average nutrient intake was of the same order of magnitude for garrison troops in the Pacific and U. S. troops in training camps in the U. S. This situation was in large part attributable to ample supplies of fresh and frozen foods which supplemented the standard non-perishable items of the regular overseas issue. Troops living exclusively on packaged rations had almost the same nutrient intake as garrison troops because the packaged rations were quite palatable to them. Scores in tests of physical fitness were at a high level in troops who had recently survived in combat, and were less good in rear areas. Distribution curves for the data on hemoglobin, plasma protein, urinary chloride, urinary ascorbic acid, urinary thiamine and urinary riboflavin were very similar for U. S. troops in the Pacific and U. S. and Canadian infantry in North America. On the basis of clinical findings and biochemistry no cases were seen of any classical nutritional deficiency syndrome. Skin diseases, especially heat rash and epidermophytosis, were common, more so in forward than in rear areas. Moderate weight loss

averaging up to 10 pounds was found in troops recently in combat but not in garrison troops.

5. The Canadian team operated in the Mohand area of the United Provinces and in the Burmese areas of Monywa, Alon, Meiktilla, Thazi, Pegu, Rangoon and Mingladon. Twenty-three different units were studied including infantry, armored corps, artillery, engineers, medical, motor or animal transport, pioneers and Japanese prisoners. The main racial groups included Gurkhas, Punjabis, Sikhs, Rajputs, Mahrattas, Bengalis, Jats, Pathans, Waziri, Dogras, and Bihari. Their average length of service in forward areas was 21 months. Nutrient intake was difficult to estimate, but as compared with the intake of North American troops the available animal protein, riboflavin and ascorbic acid were low, the other important nutrients not differing significantly. Racial and religious peculiarities of diet are discussed. Distribution curves for hemoglobin, serum protein, serum ascorbic acid, urinary thiamine, urinary riboflavin and urinary N^1-methylnicotinamide showed many differences between Indian troops and troops in North America. The Indians had lower values for hemoglobin, serum protein, serum ascorbic acid, urinary ascorbic acid and urinary riboflavin. Curves for serum chloride, urinary thiamine and urinary N^1-methylnicotinamide were about the same. As judged by clinical findings and biochemistry no cases were seen in Indian troops of classical nutritional deficiency disease syndromes. An ocular lesion fully described in the text was present in about half of the men examined. It consisted of proliferative lesions of the sclera, with corneal changes but was not clearly related to any of the biochemical measurements.

6. Recently captured Japanese prisoners of war in Burma revealed many positive physical signs, especially weight loss, and low biochemical status, including low levels of hemoglobin and serum protein and very low excretion of riboflavin. Diagnoses were made of chronic caloric deficiency, anemia, ariboflavinosis and in one case, pellagra.

7. A regiment of Gurkhas had superior physical fitness and few positive physical signs. At the same time they had considerably lower values for serum protein and urinary excretion of riboflavin than have North American troops, and values for their serum and urinary ascorbic acid and hemoglobin were somewhat lower. It is concluded that excellent fitness and tactical efficiency are compatible with what by ordinary North American standards are low levels of several important constituents of the body notably riboflavin, serum protein and ascorbic acid.

8. The effects of environmental stress are illustrated. Among U. S. troops under stress of combat compared with those not exposed to stress complaints referable to the skin, gastrointestinal tract and neuromuscular systems were more frequent, as were positive physical findings. Their weight was lower, but biochemical status was about the same and physical fitness was actually higher in the groups under stress. Two Indian units are contrasted, one a mule transport and the other a motor transport both operating in the same area and issued the same rations. The mule transport unit showed more positive physical findings than the motor transport unit and had a lower biochemical status and inferior

efficiency. The cause for this situation was in part a ration inadequate for the work they had to do and the stress they had to face.

9. "Tropical deterioration" is discussed. In the present surveys many areas were visited where good health had been maintained among adult populations when diet was ample and tropical diseases were well controlled. White troops were efficient after continuous presence for as much as two years in severe tropical environments. Nevertheless, under certain well recognized types of stress not peculiar to the tropics men react and deteriorate similarly in tropical, temperate and cold environments.

10. A close correlation was demonstrated between the calculated average daily intake of ascorbic acid, thiamine and riboflavin and the urinary excretion before breakfast of these vitamins.

11. Analysis of the relation between individual clinical stigmata and biochemical measurements and between clinical stigmata and physical fitness scores revealed few statistically significant correlations among positive findings in the eyes, lips, mouth and skin; urinary ascorbic acid, thiamine or riboflavin; and physical fitness scores. Such correlations as existed were on the basis of small average differences, had no apparent physiological explanation, and could not be used diagnostically in individual cases.

12. Generalizations on troop feeding are made. Important considerations are variety of food items, foods similar to those the soldier usually eats in ordinary life, the avoidance of caloric deficits, and high acceptability insured by good preparation.

13. Nutritional requirements for the tropics are discussed. No support is given to the proponents of a large intake of vitamins or a low intake of animal protein. No recommendations are made on actual allowances.

ACKNOWLEDGMENTS

Both teams received the utmost consideration wherever they went. We wish here to thank all officers and enlisted men, too numerous to single out by name, who contributed to the success of the surveys.

The Canadian team wishes to thank specifically for advice and assistance Brigadier D. Welch, Director of Research, ALFSEA, Colonel W. Hurst Brown, RCAMC, Colonel J. O'Dwyer, RAMC, Lt. Colonel John Squire, RAMC, and Major Joseph Doupe, RAMC.

The U. S. team wishes to thank specifically for encouragement and assistance Brigadier General Georges F. Doriot, QMC, AUS, Colonel John B. Youmans, MC, AUS, Lt. Colonel Thomas Ward, MC, AUS, and Major William F. Ashe, MC, AUS.

REFERENCES

Adamson, J. D., Jolliffe, N., Kruse, H. D., Mallory, D. H., Moore, T. E., Platt, B. S., Sebrell, W. H., Tice, J. W., Tisdall, F. F., Wilder, R. M., and Zamecnik, P. C. (1945) Can. Med. Assoc. J. 52, 227.

Adolph, W. H., Greaves, A. V., Lawney, J. C., and Robinson, H. L. (1944) War Med. 5, 349.

AYKROYD, W. R., KRISHNAN, B. G., PASSMORE, R., AND SUNDARARAJAN, A. R. (1940) Indian Med. Research Memoirs, Calcutta 32, 84.
BERRYMAN, G. H., AND CHATFIELD, C. (1943) J. Nutrition 25, 23.
BERRYMAN, G. H., AND HOWE, P. E. (1944) J. Nutrition 27, 231.
BERRYMAN, G. H., HENDERSON, C. R., FRENCH, C. E., AND HOWE, P. E. (1944) Military Surgeon 95, 391.
CASTELLANI, A. (1938) "Climate and Acclimatization" 2d Ed., John Bale, Sons and Curnow, London.
DANN, W. J., AND DARBY, W. J. (1945) Physiol. Rev. 25, 326.
DARLING, R. C., JOHNSON, R. E., PITTS, G. C., CONSOLAZIO, F. C., AND ROBINSON, P. F. (1944) J. Nutrition 28, 273.
EDISON, A. O., SILBER, R. H., AND TENNENT, D. M. (1945) Am. J. Physiol. 144, 643.
Editorial (1944) Bull. U. S. Army Med. Dept., pp. 10–13, No. 82.
EIJKMAN, C. (1924) Lancet 1, 887.
FAIRLEY, N. H. (1945) Proc. Roy. Soc. Med. 38, 195.
FIELD, H., JR., PARNALL, C., JR., AND ROBINSON, W. D. (1940) New Eng. J. Med. 223, 307.
HOWE, P. E., AND BERRYMAN, G. H. (1945) Am. J. Physiol. 144, 588.
JOHNSON, R. E. (1945) War. Med. 7, 222.
JOHNSON, R. E., HENDEDSON, C., ROBINSON, P. F., AND CONSOLAZIO, F. C. (1945) J. Nutrition 30, 89.
JOHNSON, R. E., SADOENT, F., ROBINSON, P. F., AND CONSOLAZIO, F. C. (1945) War. Med. 7, 227.
JOLLIFFE, N., AND MOST, R. M. (1943) Vitamins and Hormones 1, 60, New York.
KARK, R. M., JOHNSON, R. E., AND LEWIS, J. S. (1945) War Med. 7, 345.
KLINE, O. L., FRIEDMAN, L., AND NELSON, E. M. (1945) J. Nutrition 29, 35.
LEE, D. H. K. (1940) Papers, Dept. of Physiology, University of Queensland, Australia, Vol. 1, No. 5, 31 Dec.
LEE, D. H. K. (1944) Papers, Dept. of Physiology, University of Queensland, Australia, Vol. 1, No. 8, 29 May.
LEITCH, J. N. (1930) Dietetics in Warm Climates, London.
LUSK, G. (1931) The Science of Nutrition, 4th Ed., Philadelphia, Pa.
MACHELLA, T. E. (1942) Am. J. Med. Sci. 203, 114.
MACHELLA, T. E., AND MCDONALD, P. R. (1943) Am. J. Med. Sci. 205, 214.
MARTIN, C. J. (1930) Lancet ii, 561, 617, 673.
MCCARRISON, R. (1936) Nutrition and Public Health, Cantor Lectures. Royal Soc. Arts, London.
MILAM, D. F., AND ANDERSON, R. K. (1944) Southern Med. J. 37, 597.
MILLS, C. A. (1945) Am. J. Trop. Med. 25, 59.
NICHOLLS, L. (1938) Tropical Nutrition and Dietetics, London.
PETT, W. B. (1945) Canad. J. Pub. Health 36, 69.
PITTS, G. C., CONSOLAZIO, F. C., AND JOHNSON, R. E. (1944) J. Nutrition 27, 497.
PRICE, A. G. (1939) White Settlers in the Tropics, Am. Geographical Society, New York.
REEN, A. C. (1942) Am. J. Trop. Med. 22, 127.
RIGGS, E., PERRY, H., PATTERSON, J. M., LEESON, J., MOSLEY, W., AND MCHENDY, E. W. (1943) Can. J. Pub. Health 34, 193.
SARETT, H. P., AND PERLZWEIG, W. A. (1943) J. Nutrition 26, 611.
SHATTUCK, G. C. (1938) Comptes rendues, Congrés Internatl. de Geogr. Amsterdam Vol. 2, Section III, c, p. 327.
SINCLAIR, H. M. (1944) Am. J. Pub. Health 34, 828.
SNEDECOR, G. W. (1940) Statistical Methods, Iowa State College Press, Ames, Iowa.
SQUIRE, J. (1945) Personal communication.
TAYLOR, G. F., AND CHUTTANI, P. N. (1945) British Med. J. 1, 800.
VAN VEEN, A. G. (1942) Ann. Rev. Biochem. 11, 391.

YOUMANS, J. B., PATTON, E. W., AND KERN, R. (1942) Am. J. Pub. Health 32, 1371.
YOUMANS, J. B., PATTON, E. W., AND KERN, R. (1943) Am. J. Pub. Health 33, 58.

The results of many studies on troops are not available in published form, but in some cases reports may be obtained by direct application to the appropriate governmental agency. Sources used in preparing the present paper include:

1. Armored Medical Research Laboratory, Fort Knox, Kentucky, U. S. A.:

a. "Final Report on Project No. 30, Test of Acceptability and Adequacy of U. S. Army C, K, 10-in-1 and Canadian Army Mess Tin Rations," 22 November 1944.

2. Associate Committee on Army Medical Research, National Research Council, Ottawa, Canada:

a. "Field Test Trials of Rations, Penobsquis, New Brunswick, 1943."

b. "Ration Trials, Prince Albert, Saskatchewan, January–March, 1944."

c. "Report on the Nutritional Status of I.O.R.'s—Fourteenth Army, Canadian Nutritional Research Team, RCAMC, G. Research, ALFSEA."

3. Harvard Fatigue Laboratory, Morgan Hall, Boston, Mass., U. S. A.:

a. "The Nutritional Status of Enlisted Men in the Desert Training Area," 15 October 1943.

b. "Laboratory Manual of Field Methods for Biochemical Assessment of Metabolic and Nutritional Condition," March, 1945.

4. Medical Nutrition Laboratory, Army Service Forces, Chicago, Ill., U. S. A.:

a. "Report of Nutrition Survey in Pacific Theater of Operations, April–June, 1945," 22 August 1945.

5. National Health and Medical Research Council, Fatigue Laboratory, Sir William Macgregor School of Physiology, University of Queensland, Australia:

a. "Open Report No. 1—Physiological Considerations in the Development of Tropical Centres."

b. "Open Report No. 3—General Aspects of Tropical Fatigue as Seen in RAAF Ground Crew, Fourth Report of Field Investigation into the Incidence of Tropical Fatigue."

NEUROLOGICAL CONDITIONS RESULTING FROM PROLONGED AND SEVERE DIETARY RESTRICTION[1]

(Case Reports in Prisoners-of-War, and General Review)

D DENNY-BROWN, M D, F R.C P.

TABLE OF CONTENTS

I. INTRODUCTION

The confinement of large groups of men in close captivity in war prison camps, on extremely limited diets for long periods of time, has unwittingly provided data on the effect of dietary insufficiency, on a scale that experimental medicine can hardly hope to emulate. Unfortunately, the conditions were seldom such that accurate data as to the food values and contents could be plotted against the resulting clinical and pathological effects. In Changi Camp in Singapore, the inclusion of a full British field hospital, with the addition of a biochemist trained in agricultural research in food and accessory factors resulted in the maintenance of detailed accurate records for the whole period of three and a half years of captivity. In Batavia and Siam (Thailand) valuable data were also gathered by medical officers in various prison camps Some of these records are already in course of publication and it is hoped that all will soon be available. A number of interesting conditions was observed in relation to deficiency of thiamin, riboflavin and niacin. A number of others occurred in which deficiency of these substances played a doubtful part, though dietary factors were

[1] From the Neurological Unit, Boston City Hospital and the Department of Neurology, Harvard Medical School

certainly at fault. Since these latter conditions include varieties of nervous disorders of which not only mechanism of causation but also the clinical classification is in doubt, the experience of a neurologist who was in a position to review a number of such cases soon after their release from different camps is here set forth.

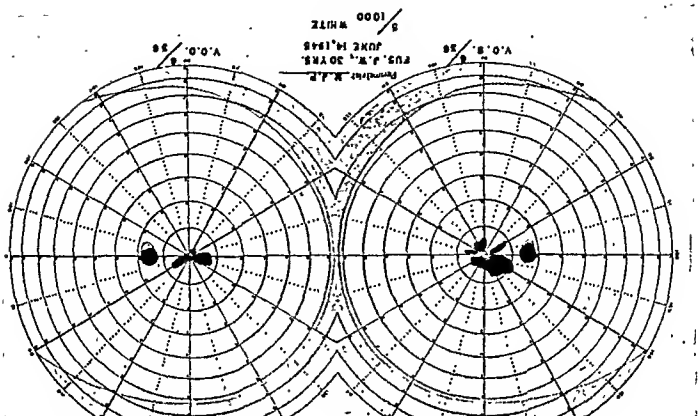
The author was Consultant in Neurology to *India Command* and to *Allied Land Forces, South East Asia* during the period covering the release of prisoners-of-war from Rangoon, then Malaya, Singapore, Thailand and Batavia. Those British and Indians who were disabled in any way were brought to military hospitals in India where those with neurological disability were examined by the author.

II. GENERAL DATA ON CASE MATERIAL

1. Cases Following Captivity in Burma

In the course of routine inspection of hospitals in early June 1945 a group of sick British ex-prisoners-of-war, recently released from captivity in Rangoon was briefly examined by me in hospital in Secunderabed in India. Their diet had been of parboiled rice with two or three small pieces of meat a week in a daily vegetable "green stew" containing also the grains *dahl* or *gram*. In the three months before release the quantities of food had improved and one or two eggs a month had been obtained in the last two years. Records of exact quantities were not kept by this group, but the syndromes found served to draw attention to the neurological problems.

Only 235 British sick, from a total of some 650 British prisoners required hospital treatment on release from Rangoon. In this group only one example of severe nutritional edema was seen, a score of heliotrope tongues, several instances of recovering beriberi, one moderately severe. Edema of the ankles without abnormal neurological signs was common. The proportion of neurological disorder was therefore very small and the majority were suffering from malaria, chronic dysentery, and helminth infestation. Twenty-three of these patients however complained of loss of vision for reading. After elimination of those who had lost spectacles, or who had developed errors of refraction, there remained 14 suffering from a central scotoma (figs. 1 and 2) and 9 of these had pallor of the temporal sides of the optic discs. 3 of these were grossly ataxic in gait. Vision was reduced to a degree varying from 6/9 to 6/60. Six of these had mild evidence of corneoscleral vascularity, not in proportion to the loss in vision. Two patients had slight residual neuritic beriberi (weakness in dorsiflexion of the feet, wasting of the legs and absence of ankle jerks). Three had ataxia in walking, with loss of sensation of position in the feet, gross loss of vibration sense in the lower limbs, but no muscular wasting or weakness. One had severe bilateral nerve deafness. These patients gave histories of the onset of these disorders 8 to 15 months after capture, with rapid deterioration of vision in the course of 1 to 3 weeks, with little further change. Unsteadiness of gait appeared at the height of the illness. Four of these cases were referred to



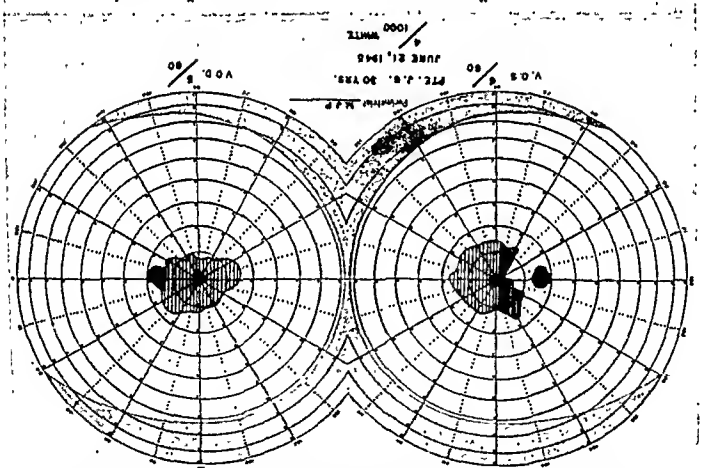


FIG. 1. (top) VISUAL FIELDS OF CASE 1 (CITED IN APPENDIX)
The area shaded by vertical lines is of relative central scotoma. Within this is a small area of absolute scotoma covering the fixation point.
FIG. 2. (bottom) VISUAL FIELDS OF CASE 4

the Army Neurological Centre for close investigation, and a summary of the pertinent data kindly sent me by Major Parsonage is given in the Appendix (cases 1–4). Lumbar puncture in 4 of the most disabled cases revealed no

abnormality of the spinal fluid, blood counts showed no significant anemia, X-rays no change. Hookworm ova were present in the stools of 2. The remaining patients were embarked in hospital ship for Britain. Spillane (215), Garland (80) and Shapland (201) have referred to cases of retrobulbar neuritis and ataxia from the same group. In the following months 4 Indian soldiers released from Rangoon and still suffering from severe retrobulbar neuritis and ataxia were observed by me in other hospitals in India, with numerous examples of mild retrobulbar neuritis of the same type.

2. Cases from Singapore, Malaya and Thailand (Siam)

With the end of the Japanese war in August 1945, and the release of over 200,000 prisoners of war (including some 150,000 Dutch) in Singapore, Malaya, Siam, Batavia, Sumatra, and Indo-China, most of the British and Indian nationals who were still sick were rapidly evacuated to India, where hospitals in three main areas were evacuated to receive them. Directives were issued drawing attention to the conditions of retrobulbar neuritis and ataxia. In view of the lack of effect of thiamin, and the greater improvement reported earlier by Landor and Pallister (126) to be produced by liver extract than yeast concentrates, intramuscular liver extract was recommended in treatment. The similarity of the spinal ataxia to subacute combined degeneration of the spinal cord suggested that full dosage would be required, as in the latter disease. With some help in preliminary sorting of cases by Lt. Cols. Walter, Turner and Elliott, I was able to see every case of neurological disorder in 3667 sick received in India in the months of September and October and examined many of those not so classified. These cases were seen in military hospitals in Bangalore (Jalahalli), Ranchi, and Dinapore. I am permitted to quote the data reported here from my official report.

It is difficult to estimate the proportion this group of 3667 represent of the surviving prisoners. The total British and Indian prisoners released numbered about 60,000. A few of the seriously ill patients remained under treatment in Singapore, Bangkok, and in Rangoon, and are not included in the group here discussed. On the other hand some 30 sick Dutch are included in the total number. The majority of these sick patients were ambulatory. Malaria, dysentery, and worm infestation were the usual causes of disability. Those severely ill were suffering from pulmonary tuberculosis, nutritional edema, microcytic and a few macrocytic, anemia. A few cases of residual disability from poliomyelitis, and one instance of dermato-myositis were seen. Night vision had been poor in many, and remained defective in a few. Xerophthalmia was not seen. Scurvy had been very rare.

The total number found to be disabled by the types of neurological disorder under discussion is shown in Table I. It will be appreciated that cases of neurosyphilis, deafness due to otitis media, injury, and other extraneous disorders were excluded. It will also be apparent that the number of cases in relation to the total number of prisoners from whom they were drawn (approximately 60,000) is very small. The European cases were British except for a group of 6 Dutch affected cases.

3. *Clinical Description*

Swelling of the ankles or below the knees, without loss of ankle jerks, without muscular wasting or weakness, was common, and allowing for its persistence for a time after full diet had been resumed, showed a reasonable correlation with low serum protein in all cases where this was estimated. The value found usually ranged between 5.5 and 6.5 grams per 100 cmm., mostly over 6 g. Extensive reports of this condition will be made by others. It will be noted that recent work on the experimental production of "famine edema" (119) indicates that damage to the capillary membrane is more important than hypoproteinemia, and only slight falls of plasma protein were found. It is essential not to

TABLE I

Residual Neurological Disability in Patients from South East Asia Received in India (Aug.–Sept. 1945)

	EUROPEAN	INDIAN	TOTAL
Total Patients Received	1,597	2,070	3,667
Peripheral Neuritis	42	68	110
Retrobulbar Neuritis	129	56	185
Spinal Ataxia	21	39	60
Deafness.	10	3	13
Laryngeal Palsy	2	1	3
Spastic Paraplegia	9	0	9

The figures given for Retrobulbar Neuritis include those for Ataxia, Deafness, and Laryngeal Palsy and Spasticity except for 4 cases of Ataxia, 3 of Deafness, 1 of Laryngeal Palsy. The total number of clear-cut neurological disorder (excluding mild and recovered states and conditions of doubtful etiology) was 303 cases

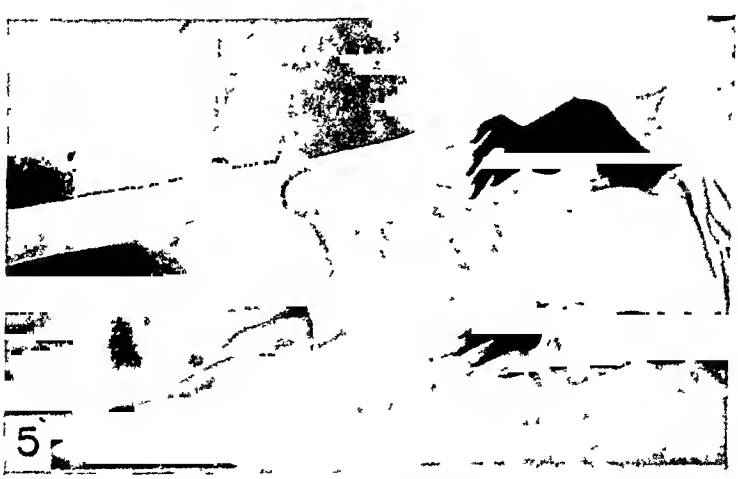
confuse this common condition with beriberi which it had often been called by medical officers and by the patients themselves. It could be very severe in degree (fig. 3) without any neurological disorder.

Beriberi. It is convenient to begin discussion of the neurological conditions with consideration of *beriberi.* The earlier descriptions of beriberi in common with the unclear nosological ideas of the times, included all manner of paralysis, edema and pains in the lower limbs. In later descriptions, besides the classical type where aching pains and tenderness in the calves herald the onset of footdrop and numbness of the outer aspect of the leg, with or without edema and cardiac involvement, peculiarities in the accentuation and distribution of neurological disorder have long been recognized. These will be discussed separately later.

In view of doubts as to the identity of some of these variants our classification first set aside cases not exhibiting a clear-cut distal neuritis. Since the conditions were in a chronic stage and had already been under treatment for 2 to 3 weeks, the presence or absence of cardiac abnormality was not used as a basis of classification. The presence of symmetrical footdrop with muscular wasting below the knee, tenderness of calf muscles, stocking area of hypesthesia, and loss

3

4



5

Fig. 3. Severe Nutritional Edema ("Famine Edema"), without Affection of the Nervous System

Note the protruberant abdomen from ascites and swollen ankles

Fig. 4. Severe Chronic Beriberi with Fixed Contracture of the Calf Muscles (Case 9)

Fig. 5. As Figure 4 to Show the Abnormal Posture of the Hands and Wrist Resulting from Contracture of the Flexor Tendons

of the ankle jerks clearly indicate a distal type of peripheral neuritis The common observation of recovering cases had convinced me that *absence of ankle jerks* and great *muscular tenderness* long persisted after recovery of sensation in the skin, and indeed, of muscular power *Weakness in dorsiflexion* of the ankle and of the great toe is very slow to recover Likewise all these three signs may be insisted upon as essential criteria in mild cases Patients with diminution or loss of ankle jerks with tender calves or burning paresthesias in the feet, but without history of foot-drop, might have mild beriberi or some nerve root or spinal cord syndrome For the purpose of the present discussion they are set aside These conditions, called "latent beriberi" by some, only confuse the issues raised by the other more important syndromes

Edema was seen in relation to cardiac beriberi in only 3 or 4 cases, and in these was related to recent exercise Tenderness of the feet accompanied beriberi of moderate degree, but was in the nature of a tenderness of the small muscles, whereas an entirely different type of *burning* tenderness of the soles of the feet, often interfering with walking, usually without signs of neuritis, was common (case 12, Appendix) No exact count was made of these cases In some cases of long persistent burning feet the tendon jerks were brisk, in others sluggish, but these signs were not interpreted as evidence of beriberi No cutaneous lesion or vascular abnormality was seen, or history of such obtained This condition was, I found, well known in early British India where it had been called "rheumatic burning of the feet" (139), but for many years now has been loosely called "beriberi" by many Subsequent data from Singapore camps which will be mentioned later show it to be completely distinct ("happy feet") Its chief distinguishing characteristic is its burning character, a soreness of the skin increased by warmth, in the manner of aeroparesthesia, erythromelalgia and related vasomotor disorders

The cases with characteristics clearly indicating a distal sensori motor neuritis were remarkably few (Table I) Among these were a few cases of very severe chronic beriberi, and here the condition was substantially a contracture of the tendo achilles with fixed foot-drop, moderate weakness of the knee and hip movements, with a very characteristic contracture of the hands ("griffe rétractile" of Jeanselme, case 9 and figs 4 and 5) Even here the disturbance was *peripheral* Sensation including vibration sense was diminished only in the periphery, and vision, speech, and hearing were not affected A large number of others, whose number was not accurately determined, but might be roughly estimated at one-tenth the total number, could give a history of foot-drop at some time or other during their captivity, with subsequent recovery, or with persisting sluggishness of ankle jerks with or without tenderness All other patients with diminished or lost ankle jerks showed the characteristics of the ataxic syndrome

Pellagra *Pellagra*, with characteristic skin and mental change was seen in only 2 patients A group of 27 mental cases was found to consist of endogenous conventional types without evidence of pellagra In all the other patients glossitis and angular stomatitis of mild degree were not uncommon,

but in severe degree were very few indeed, and these seldom associated with the nervous disorders to be described.

Retrobulbar Neuritis. The figures for retrobulbar neuritis given in Table I take no account of those in whom recovery had occurred, of whom they formed a proportion variously estimated at one-fourth to one-tenth. The large number of cases of this condition had a remarkable uniformity. Specimen case-histories are given in the Appendix (cases 1–8, 11, 13). The history given was of the development over a period of time, usually some 3 weeks but as short as one day in one patient, 3 days in several others, of an inability to see colours or small objects. A mist obscured the centre of the field of vision and gradually became so intense as to make it impossible to recognize the features of friends. In some the visual change was preceded by smarting pains in the eyes, more usually by no such sensations. In some, visual hallucinations of moving lights or movement of objects accompanied the onset. Both eyes were affected at once, though one might be a little worse than the other. When central vision was lost the condition appeared to become arrested, and no instance of complete blindness was seen. The most severely affected patients could still count fingers seen in the peripheral visual field. After the first one to 3 months the condition appeared to have reached a stationary state, or to improve, and no instance of steady progression for a longer period was encountered. Relapse following an attack of dysentery had been frequent. The greater proportion of cases had recovered vision sufficiently to be able to read newsprint, but these still complained of a liability to fatigue so that after reading for 5 or 10 minutes vision became blurred and restored only after a rest for a further 10 to 15 minutes. Those who had suffered very severe loss of vision appeared to have recovered little if any since liberation.

The visual fields showed a central scotoma usually extending towards and including the blind spot (figs. 1 and 2) (Cases 1 and 4, Appendix). Studies of the fields of mild cases by confrontation test by the author usually indicated one or more paracentral scotomata similar to those shown in fig. 2. Two patients complained of a greater visual defect below the horizontal, and these, in one by charted field and the other by confrontation test, showed scotomata which extended much further below the fixation point than above. The type of paracentral scotoma which lies between the blind spot and the fixation point (centrocecal scotoma) so commonly found in multiple sclerosis, and described in pernicious anemia, was not observed. The effects of tobacco, syphilis and quinine could be satisfactorily excluded.

The fundi in the mildest cases was of natural appearance. When loss of vision was moderate or severe the temporal side of the disc was invariably pale. In many this pallor was accompanied by some extension of the physiological cup to the extreme temporal edge with a frequency greater than is experienced in normal fundi. In many, also the retina bordering this edge of the disc was pigmented in a small crescent and in a few the appearance was as if the physiological cup extended from the disc on to the small crescentic pigmented area of retina. The vessels were of normal appearance, the lamina cribrosa was clear,

and no evidence of inflammation or swelling was present The macula and general retina were normal The only ex-prisoner of-war observed by us to have swelling of the optic discs had a history of recent headaches and deterioration of vision and was considered to be suffering from increased intracranial pressure, probably due to tumor

The pupillary reaction to light was invariably present but was of small amplitude and poorly held if optic atrophy was severe

The condition was not always absolutely symmetrical but vision was never even moderately affected in one eye without some loss in the other One patient with retrobulbar neuritis presented a raw beefy magenta-coloured tongue and a few showed evidence of mild glossitis or stomatitis

Spinal Ataxia The degree of this affection varied from a gait apparently normal except for some uneveness of height to which the foot was lifted in walking and a tendency to stagger a little in turning round (fig 6), to a disorganisation of gait so severe that the patient could not walk without assistance (figs 7 and 8) Most usually the gait was unsteady with a wide base with staggering on turning, and unsteadiness on standing with the eyes closed

The constant finding was loss of vibration sense in the lower limbs, usually in all parts below the iliac crests In several patients there was no ability to perceive vibration below the clavicles or the upper ribs In these there was some defect in vibratory perception in the upper limbs, but usually these were not affected Sense of position was also affected, but in lesser degree, so that it was impaired in the toes where vibratory sense was lost in the whole limb (case 3, Appendix) and lost completely on the toes with impairment of vibration in the trunk (case 5) In some of these patients touch and pain sensation was unaffected, but there was usually some mild impairment of both below the knees In none was complete loss of pain sensation found in any part Apart from retrobulbar neuritis in many the cranial nerves were not affected except for a subjective numbness of the face in some, a weakness in facial movement in one case (case 10), bilateral nerve deafness in 8, and aphonia from partial laryngeal paralysis in 2 cases (one with palatal weakness) (cases 11 and 13)

The tendon reflexes were variously affected In some the knee and ankle jerks were unusually brisk (case 1) Most commonly the ankle jerks were sluggish or lost, the knee jerks brisk In about a fifth of the cases both knee and ankle jerks were lost

All these patients were thin and undernourished, but, allowing for this, muscular power and bulk appeared unaffected in all but 6 of the ataxic cases In these 6 there was some wasting and tenderness of calf and pretibial muscles with absence of ankle jerks, and with weakness in dorsiflexion of ankle indicating a coincident peripheral neuritis In the remainder the absence of muscular tenderness and the excellent power of dorsiflexion of the ankle (see figs 7 and 8) caused us to doubt the presence of peripheral neuritis As subsequent discussion will show, mild impairment of pain and touch sensations below the knee associated with diminution or loss of tendon jerks are not trustworthy evidence of peripheral neuritis, for these, as well as subjective numbness, can

FIG. 6. TO SHOW THE USE OF A SINGLE STAFF BY PARAPLEGICS IN THE EAST
The patient has a moderate ataxia (case 5)

FIGS. 7 AND 8. SEVERELY ATAXIC GAIT, POSSIBLE ONLY WITH ASSISTANCE (CASE 10)
There is no footdrop, and the thinness of the limbs is solely due to inanition

certainly be caused by damage to the spinal cord alone The presence of burning sensations in the feet also cannot be accepted as evidence of peripheral neuritis, and must be set aside as an independent phenomenon which was found in about one-fifth of the cases of ataxia, and without relationship to its severity.

The plantar responses were usually clearly flexor, but in 4 of the more severe cases (see cases 2 and 11) one or both plantar responses were clearly extensor Other signs such as ankle clonus or absence of abdominal reflexes were not seen.

The spinal fluid was normal in all respects in 5 patients in whom it was examined

There was no evidence of nystagmus or of ataxia of the upper limbs or titubation The control of the sphincters was not affected except in 2 doubtful cases to be mentioned below (spastic syndrome). One patient presented marked mental apathy, 1 was disoriented and confused, and a few others had slight slowing of mental function The remainder were mentally unaffected

If recognisable ataxia was present some evidence of retrobulbar neuritis was found in all but 4 cases, and though the amblyopia was usually severe in the presence of ataxia this was not invariably so (case 11) Similarly a *severe* loss of vision was usually accompanied by some ataxia but several examples were seen where no ataxia was present or history of ataxia obtainable It was the rule to find some impairment of vibration sense on the ankles and toes if any degree of retrobulbar neuritis was present, but a few were found where such defect could not be demonstrated though vision was less than 6/36

Patients with ataxia most usually gave a history of insidious onset of unsteadiness in walking between August 1942 and early 1943 and denied the presence of foot-drop Premonitory shooting pains in the lower limbs had been experienced by a few patients and "happy feet" (burning sensation in the soles of the feet, especially at night) had preceded the onset of unsteadiness in many Some patients had suffered from foot drop at times after the onset of ataxia, but most denied having had foot-drop at any time It was thus clear that ataxia was not a residue of peripheral neuritis and was an independent affection Two instances of ataxia of rhythmical cerebellar type with titubation and dysarthria were found but were completely different from those described above and had followed cerebral malaria with prolonged hyperpyrexia, of which it is a well recognised residue

The ataxic patients were all afebrile and none had any remarkable degree of anemia A group of 20 severely anemic patients under special treatment included 3 with beriberi neuritis, several with retrobulbar neuritis but none with ataxia or spastic syndrome Very few had glossitis or angular stomatitis, or even atrophic papillae and these were of mild degree The relatively few instances of severe glossitis and angular stomatitis seen in all sick ex-prisoners had no neurological complications

The Spastic Syndrome Nine British army personnel were clearly distinguished from the ataxic cases by an extremely stiff legged gait with spontaneous ankle clonus when the foot touched the ground (cases 7 and 8 and figs 9 and 10) The legs tended to cross in adduction (fig 9) and in passive movement

exhibited the clasp knife rigidity of spasticity. The knee and ankle jerks were extremely brisk and led to patellar and ankle clonus respectively. The plantar responses were extensor. In 2 cases the tendon jerks in the upper limbs were also extremely brisk, and in one of these the flexors of wrist and elbow were spastic, speech was spastic and facies expressionless (case 8).

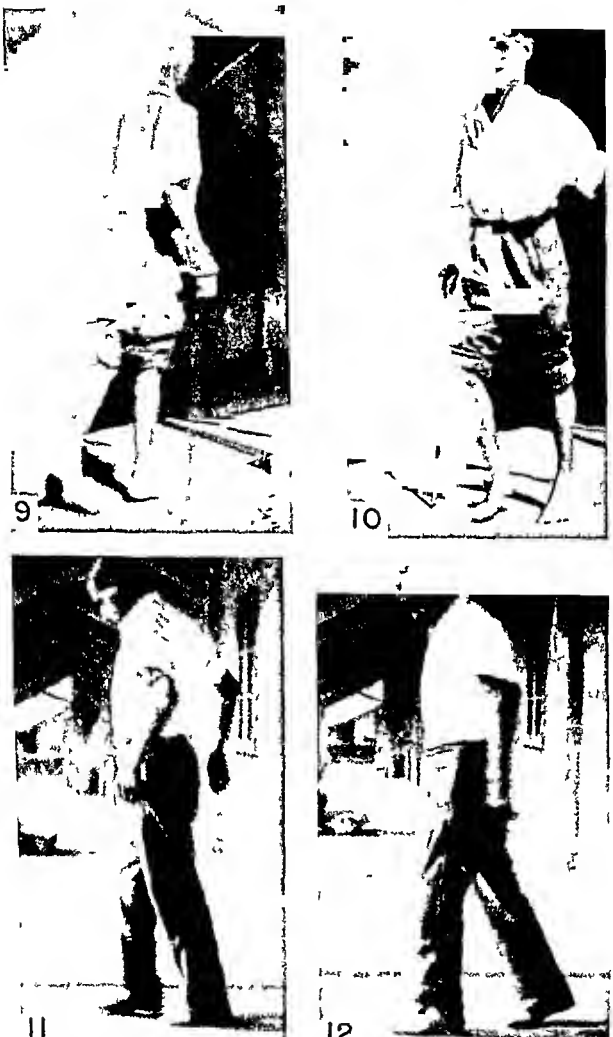
None of these 9 cases showed loss of sensation of any kind, or wasting of muscles. All had some evidence or history of retrobulbar neuritis, severe in 1 patient.

The onset of this spastic condition had been between August and December 1942 in Changi camp, Singapore, in all, and had been gradual and insidious. In 3 the illness had commenced with a confused mental state for which there is now amnesia, and these 3 had each had one or more convulsions since. There was no history of hallucinations. The present mental state was normal in all. This affection, which bears a close resemblance to, if not identity with, lathyrism, had therefore some clinical evidence of a cerebral pathology in 3 cases. The initial paralysis had affected the upper limbs as well as the lower in 5, but spasticity of the arms remained in only 1 case. Incontinence had been present in 4 and remained in 2. Diplopia had occurred in the early stage in 2, but no strabismus now remained.

Another British soldier was seen by us in September 1945 in an illness of about 8 weeks duration characterised by daily low fever (97–99 of), mental apathy, with disorientation in place and time, catatonic preservation of attitudes, and severe general weakness. No mucous or cutaneous lesions were present. The optic fundi were normal, there was no strabismus or nystagmus, or other cranial nerve abnormality. The tendon jerks were all brisk and plantar responses extensor, without sensory loss. B.P. 140/110 mm. The cerebrospinal fluid showed a pressure of 250 mm., 81 r.b.c. and 2 lymphocytes, total protein 40 mlgm. The blood Wassermann was negative. Hemoglobin 89 per cent. This condition was considered to be probably an initial stage of the spastic paraplegia.

Transitional States. It has already been mentioned that 4 patients with spinal sensory ataxia exhibited extensor plantar responses. Only 1 of these exhibited any trace of spasticity, and that only by his stiff manner of walking, his limbs being loose on passive manipulation and the tendon jerks sluggish. Four others with a stiff but grossly ataxic gait had either very active or absent knee jerks, but absent ankle jerks and flexor plantar responses, besides the usual loss of vibration and position sense. The gait of one of these (case 11 in Appendix) is shown in figs. 11 and 12.

One British officer who gave a history of several relapses and remissions of spasticity and loss of vision since August 1942, presented inactivity of the pupils to light, normal optic discs, and a mild spastic paraplegia without sensory impairment. He had had one recent convulsion. This case, by reason of the relapses and pupillary change was possibly of other origin and was not counted in the statistics. The spinal fluid was subsequently reported normal in cells and protein and Wassermann negative. A British soldier gave a history of spastic paraplegia in July 1943 with recovery by April 1944, and retrobulbar



FIGS. 9 AND 10 SPASTIC PARAPLEGIA WITHOUT SENSORY LOSS (CASE 7)
Note the adduction of the knees and the inability to lower the heels to the ground

FIGS 11 AND 12 SPASTIC ATAXIC GAIT (CASE 11)
Though the tendon jerks were absent and the limbs could be relaxed completely when lying in bed, each leg was moved stiffly in walking and developed a clonic tremor in the end of forward movement in the step

neuritis in August 1944 with subsequent recovery. He now showed only mild peripheral neuritis. Another reported a spastic paraplegia from September to December 1942 with complete inability to walk for 2 months and impaired vision for 3 months of this period, with good subsequent recovery except for a renewed retrobulbar neuritis 18 months before release. Very brisk tendon jerks and pallor of the optic discs were the only residual signs.

Apart from these variants the syndromes of sensory ataxia and spastic paraplegia were remarkably uniform.

Deafness. Eight of the most severely ataxic patients suffered from deafness of central type. Five others suffered from retrobulbar neuritis without ataxia, and deafness of the same type. The onset of this symptom had been gradual, and most usually months or years after other symptoms, without change in existing retrobulbar neuritis or ataxia (cases 2 and 13). No audiograms were available but it was clear that in none was deafness complete. In a quiet room a loud speaking voice could usually be heard, but in a ward any extraneous noise appeared to make speech incomprehensible. Tinnitus was usual but there had been no vertigo. The tympanic membranes were of natural appearance. One of these cases, though unable to hear ordinary speech, was recognised by the other men as unusually acute in picking up the noise of aircraft.

Laryngeal Paralysis. In 3 patients the voice was of a blowing quality owing to incomplete approximation of the vocal cords. Laryngoscopic examination confirmed that this was the case with weakness of both adduction and abduction of the vocal cords. This condition was associated with marked ataxia and retrobulbar neuritis except in one unique case where the laryngeal disorder had preceded the development of a peripheral wasting and fibrillation in the limbs. It is felt that the condition was indeed progressive muscular atrophy in this patient for the atrophy and fibrillation were characteristic in spite of some 4 weeks of full diet with vitamin supplements, though the glossal and palatal wasting of that disease were still absent. There was no retrobulbar neuritis but the patient complained of night blindness without retinal change. The onset of laryngeal paralysis had been recent (1944–45) in the few patients in whom it occured, and had been gradual over a period of weeks without change in other symptoms. Dysphagia was also present in one case (a patient with retrobulbar neuritis, deafness, ataxia and footdrop in addition), but there was no nasal regurgitation or palatal weakness, and the onset of aphonia had not occurred with his beriberi neuritis (case 13).

Asymmetrical Palsies. A few examples of persistent paralysis of one side of the face, or of weakness and wasting of the muscles of the shoulder girdle on one side were seen. These were not related to the disorders mentioned above, and were regarded as incidental examples of Bell's palsy, or of brachial neuritis. There was no evidence that nutritional deficiency had predisposed to such asymmetrical neurological conditions.

Corneal Degeneration. It was noted that in 3 or 4 cases of retrobulbar neuritis the cornea was irregular though clear. No cases of corneal opacity were

seen, but neither of these conditions were specially segregated by us and others will report on their general incidence

4 *Data Concerning the Onset of Neurological Disorders*

(Information from Medical Officers of Camps in Singapore, Batavia and Thailand)

The neurological disorders that have been described were the residual signs of a prolonged state which underwent a gradual evolution, and was already considerably modified by the changed conditions and nutrition since release Some interesting facts in their manner of development were recorded by the medical officers of prison camps, notably the staff of a British Army Base Hospital captive in Singapore (Changi Hospital) and of Cycle Camp, Batavia It is to be hoped that the full version of these officers, so faithfully recorded and kept through years of hardship, will soon be published * It is necessary here only to refer to some general conclusions necessary for the better understanding of the conditions concerned, and to correlate the neurological data

Report from Changi Camp, Singapore In this complete and detailed account it is clear that the various disorders described made separate and independent appearance The number of prisoners in the camp varied greatly owing to transfers of working parties and to other camps In 1942 the number of British prisoners varied between 35,000 and 8,000 and the number of Australians from 3,000 to 12,000 Beriberi began in March and April 1942 with an incidence of 35 9 per 1,000 Glossitis, with an incidence of 4 38 per 1,000 began in May 1942, dermatitis of the scrotum began in mid July and was extremely common (28 4 per 1,000) These muco cutaneous conditions, with a few incidental cases of pellagra (1 2 per 1,000) responded well to marmite (yeast extract) Pains in the feet ("happy feet") began by the end of August 1942 (12 6 per 1,000) and responded well to nicotinic acid (niacin) Also at the end of August there commenced degeneration of the cornea (9 5 per 1,000) retrobulbar neuritis (5 4 per 1,000) and spastic paraplegia (1 4 per 1,000)

Retrobulbar neuritis increased steadily in frequency through September to December when increased nicotinic acid and riboflavin in the diet were resulting in a marked falling off of glossitis, scrotal dermatitis and painful feet, and beriberi had dropped to only 12 cases a month (December) for the whole camp. Fresh cases of retrobulbar neuritis became numerous in April and May 1943 when mucocutaneous lesions and beriberi were subsiding in frequency. The incidence of burning soreness of the feet followed that of mucocutaneous lesions but with a time lag of about one month Cases of granular degeneration of the cornea paralleled those of "burning feet" but with a much smaller incidence

There is no mention of the ataxic syndrome as such and these cases appear to have been included under beriberi for it is noted that unsteadiness of gait without loss of tendon jerks, with loss of vibration sense, and with numbness of

* See Hobbs, H E , and Forbes, F A , Lancet 2 149–153 (Aug 3) 1946 Cruickshank, E K , *ibid* 2, 369–372 (Sept 14) 1946 and Burgess, R C , *ibid* , 2, 411–418 (Sept 21) 1946

limbs extending on to the trunk, in some numbness round the mouth, occurred frequently in the later examples of that disease (Captain Cruickshank). The subject was discussed by the medical officers and it was further noted that whereas painful cramps in the calf muscles had been infrequent in beriberi in 1942 the patients with later onset of "beriberi" frequently complained of painful cramps preceding numbness and unsteadiness in gait.

From August 1942 onwards the "spastic syndrome" gave much concern. From then to February 1943 there were 37 cases of "spastic encephalopathy," difficult to differentiate from Wernicke's acute encephalitis which continued to occur in a few cases. Major P. R. Graves, R.A.M.C., described this "spastic encephalopathy" as beginning with difficulty in walking and pains in the legs and spine. Later, mental dulling, dimness of vision, diplopia, and spasticity appeared. Major Graves later submitted an analysis of 29 cases personally observed and 34 other cases, of all grades of severity. Six cases terminated fatally after courses of 3, 8, 17 and 18 days, and 1 year in 5. The 6th succumbed to pulmonary tuberculosis. Many of the milder states amounted to increased tendon jerks with ankle clonus, and usually an extensor plantar response, in the course of dysentery or prolonged fevers. These recovered without incident. Six of the severe cases with dilirium also recovered. Spastic difficulty in walking occurred in 54 per cent, amblyopia in 46 per cent, mental changes in 41 per cent, burning pain in the feet in 38 per cent, paresthesias in 17 per cent, pain in the spine in 6 per cent and diplopia in 5 per cent. Epileptic seizures in the acute stage occurred in 2 cases, cramps in 3 cases. Lumbar puncture in 6 of the severe cases showed invariably normal cell count and protein content. Granular cornea was reported in one case, stomatitis in a few cases, and pellagrous skin lesion in one case. In one patient some athetoid movements and tremors characterised the confused period, recalling "typhoid pellagra." Diplopia when it occurred was a fleeting transient early symptom unaccompanied by any objective strabismus or nystagmus. Aphonia with palatal palsy developed at the height of the illness in one case. Sensory loss was not demonstrable in any of the cases. The tendon jerks were invariably exaggerated. Fever to 102° F and 104° F was often associated with the delirious phase. One patient developed paranoid ideas, another became elated, in the stage of delirium but hallucinations were not mentioned. The disorder progressed, sometimes to a fatal termination, in spite of parenteral thiamin (2 mgm. daily intravenously), niacin (1.7 cc. nicamide intramuscular plus 1.7 cc. by mouth daily), marmite (yeast concentrate in dosage of 2 oz. daily), and intramuscular liver extract in some. Larger dosage was not available, but the failure to react to the doses mentioned was clearly documented. Autopsy in 4 fatal cases revealed "small translucent dots" scattered about the white matter of the frontal and occipital lobes, to a less extent the parietal lobe. These small areas were 2–3 mm. in diameter and had the appearance of "sago grains in milk." No change was seen in the brain stem or spinal cord. The only other autopsy finding of note was a superficial erosion of folds of mucosa in the colon. Williams (260) speaking of another case mentions small translucent degenerative areas in the tracts of the spinal cord.

The onset of spastic rigidity was rapid, occurring in the course of 1 to 3 days after 1 to 3 weeks of illness. In severe cases a bilateral hemiplegia, the arms rigidly flexed across the chest and legs rigidly extended, with dysarthria, dysphagia, and expressionless facies, was constant at this stage. Incontinence of urine and feces also then occurred. One patient made a complete recovery, except for residual briskness of reflexes, from such a state.

Wernicke's encephalopathy was rare after the first few months, but its acute onset with vomiting, nystagmus and mental confusion differentiated it from "spastic encephalopathy." It was stated that on the diet available at least one patient recovering from Wernicke's encephalopathy and still receiving thiamin developed "peripheral neuritis". Fresh cases of spastic paraplegia occurred steadily through 1943 (52 cases) when beriberi had fallen off very considerably.

Major Graves observed 3 prisoners who developed unique symptoms in August 1945 just as the period of captivity ended. All 3 had been supplementing their diet with quantities of tapioca flour. The thiamin/non-fat calorie ratio of the diet at the time (apart from the tapioca supplement) was 0.36 on a total caloric value of 1600. Each of the 3 patients developed drooping of the eyelids from midday onwards, with complete relief next morning, fleeting diplopia and inability to hold the head up during the evening. Bilateral ptosis was the only constant sign. In view of the resemblance of the condition to myasthenia gravis injections of physostigmine gr. 1/100 with atropine gr. 1/100 were tried, but without effect. Parenteral thiamin 50 mgm. daily was given, and the symptoms completely disappeared in all 3 patients within one week.

The careful analysis of the diets month by month made by Major R. C. Burgess, R.A.M.C., Nutrition Officer, and Captain Simpson, Malayan State Service, Biochemist, indicated a deficiency in protein and fat*, particularly from February to October 1942. The deficiency was however not consistently extreme in any one primary dietary constituent in following months. The number of fresh cases of retrobulbar neuritis or spastic syndrome did not correlate with paucity of protein fat or carbohydrate, or of estimated deficiency in thiamin or niacin intake. Though there was a more general relationship between these syndromes and ariboflavinosis a number of inconsistencies cannot be overlooked. Fresh vegetables were scarce until December 1943 and usually absent in the hot months, and this has been commented upon by others (36)*. Numerous mucо-cutaneous symptoms occurred when the level of intake of riboflavin fell below 0.3 mg. per 1000 calories. Burgess was able to predict the increased incidence of beriberi when the Thiamin/Non-Fat Calorie Ratio (calculated by the method of Williams and Spies) fell below 0.3. In June 1941, this ratio was 0.26, and remained at or below this level until October of that year. Though the ratio was raised by an increase in Soya bean ration that month, and by the contribution of the vitamin extraction centre set up by the medical officers, it thereafter remained near 0.27 until the end of 1944, when 1170 cases

* A detailed dietary analysis for the whole period with graphs of incidence of various syndromes has been published since this paper went to press (Burgess, R. C. Lancet 2: 411–419, Sept. 21, 1946).

7. In Malang Camp no single case of retrobulbar neuritis was reported. An extra supply of canned meat was on the ration.

8. A large supply of carbohydrates in the ration provoked an earlier onset of retrobulbar neuritis.

9. Treatment by supplement of 3 eggs a day if available produced very good recovery of retrobulbar neuritis. Meat, fish, or liver also resulted in improvement but not so clearly as eggs.

10. Treatment with yeast gave improvement in some cases.

11. Treatment with thiamin, riboflavin, niacin, Vitamin C failed to bring any improvement. Quinine had an adverse effect.

"Camp dizziness" and "camp deafness" were described fully by Dr. Kuilman, R.L.V.G.I. of Batavia. Four hundred and twelve cases of periodic *aural vertigo*, in attacks occurring at varying frequencies from one a week to several a day, were observed between July 1944 and August 1945. In most there was no defect in heaving but of 43 cases of progressive bilateral deafness 37 suffered from vertigo. Many suffered from "burning feet," but very few suffered from retrobulbar neuritis, beriberi, or muco-cutaneous lesions, which were considered to be unrelated disorders. There is no mention of ataxic gait. Spasticity was not observed. The vertigo responded to treatment with yeast.

Detailed accounts of these conditions as observed in *Thailand* are not yet available. In the records of medical conferences held in one of the camps in that country during captivity Majors W. E. Fischer, A.A.M.C. and A. R. Hazelton, A.A.M.C. contributed observations on retrobulbar neuritis which make it clear that the conditions there behaved as in Singapore. A home-made ophthalmoscope was constructed and early papillitis was seen in some cases. Eggs were found beneficial in treatment. Pellagra had been common in 1943–44 in this area and ataxic paraplegia had been found in some of these cases. In October 1944 the total protein in the diet was 12 grams a day and all derived from vegetables. Nearly every prisoner of war had swollen ankles at that time.

When the prison camps in Singapore, Malaya, Thailand and Batavia were relieved in August 1945, the residual neurological conditions remaining included remarkably small numbers with serious disability. The diets had improved very considerably in the preceding three months, and all milder cases of beriberi had recovered or were recovering rapidly. The other neurological conditions showed very little improvement if any. The most convincing improvement in retrobulbar neuritis and in spinal ataxia followed treatment by intramuscular injections of crude liver extract, but was moderate in degree in the first four weeks following which the patients were no longer under our own observation.

III. REVIEW OF HISTORICAL CONSIDERATIONS

The conditions Beriberi, Pellagra and Lathyrism are all ancient diseases. In each a diet predominantly of cereals is associated with damage to the nervous system. The nervous disorders in ex-prisoners-of-war in Burma, Thailand (Siam) Malaya, Batavia and Singapore were in the nature of peripheral neuritis, retrobulbar neuritis, spinal ataxia, spasticity, deafness, laryngeal paralysis,

painful feet and a few instances of a myasthenic syndrome. In our material it is evident that each type of disorder could make independent appearance and remain either as isolated disability or in various combinations. Some of these disorders resembled what has occasionally been described in beriberi or pellagra, others suggested lathyrism. It is therefore pertinent to enquire into the circumstances of their appearance and relationship as observed by others.

1. Beriberi

Some of the classical accounts of beriberi (Malcolmson (138), Dangerfield (59), Jeanselme (111)) fail to recognize aphonia as a complication of the neuritis of beriberi. Nor is there any mention in the ancient Chinese literature (Hou and Yu (102)), though James Bontius (27) in the first European account of the disease in 1629 mentioned loss of voice. Since Hirota's account of infantile beriberi in 1898 aphonia has been a well recognized feature appearing late in the course of infantile beriberi. Bentley (20) described laryngeal affection in more severe forms of the disease in 1893, and Vedder (245) states that it occurs with some frequency in chronic adult cases. Since respiratory difficulty, attributed to edema, is a prominent feature of the disease (cf. the early name "hydrops asthmaticus") it is possible that the laryngeal condition may have been overlooked. Alcantara and de Ocampo (6) state that edema of the vocal cords is common and that, even in infantile beriberi, paresis or immobility of the cords accounted for only a proportion of cases of aphonia. Gerrard (84) found aphonia common in acute fulminating adult cases of undoubted beriberi, and Wright (278) found many degenerated nerve fibres in the recurrent laryngeal nerve, fewer in the main trunk of the vagus, at autopsy in an adult case, fully described. Kanasugi (116) cited 7 cases with illustrations of the larynx, but gave no details of the clinical state. In the case presented by Miura (155) there was foot-drop and loss of reflexes. Facial paralysis, nystagmus and aphonia developed in the 6th week of the disease. Partial degeneration of the recurrent laryngeal and vagus nerves was found at autopsy. Dürck (67) describes degeneration of the vagus in acute severe beriberi. Pekelharing and Winkler (177) state that laryngeal palsy was frequent in their Batavian patients and noted in addition 5 cases of facial and 1 of external rectus paralysis. Wright (280) later stated that he had seen affection of the 5th, 7th, 9th, 10th, 11th and 12th cranial nerves in beriberi. Winans (262) reports aphonia as a frequent symptom complicating the polyneuritis of acute deficiency states, such as accompany intestinal obstruction, in temperate climates. Aphonia therefore can be accepted as an unusual and late symptom of beriberi neuritis, and Albert (5) notes that it long persists after other symptoms have been cleared by treatment by thiamin or rice polishings.

Retrobulbar neuritis has been reported in beriberi by many Japanese since Hori (1887) (quoted by Kagawa (115)) first described the condition. Malcolmson (138), Vedder (244, 245), Pekelharing and Winkler (177) and others fail to mention any affection of vision, though it is inconceivable that such a striking symptom should have escaped notice. Scheube (191) quotes Brazilian authors.

Bentley (20) describes one case where dimness of vision long preceded an atypical beriberi. Jeanselme (111) stated that he had never seen scotoma, aphonia or other cranial nerve palsies in his experience in Annam and doubts their connection with the neuritis of beriberi. Walshe (253) found no cranial nerve lesions in beriberi in Mesopotamia in the 1914–18 war. Several Japanese (Masuda 1917, Ishida 1918, Funakawa 1921, Koyanagi 1926 and Ichikawa 1929 cited by Kagawa (115)) have also doubted the relationship of retrobulbar neuritis to beriberi, suggesting various toxic causes, or such diseases as multiple sclerosis. It is therefore necessary to examine more closely the condition called "beriberi scotoma" or "beriberi amblyopia" by the Japanese.

According to Yamaguchi (283) and Kagawa (115) the "beriberi amblyopia" of the Japanese, as originally described by Kono in 1895, Ichihara in 1902 and others in Japanese is an *early* symptom of the disease, and a diffuse degeneration of the optic nerves was shown in fatal cases by Kagoshima in 1918. The scotoma was truly central, and extended to the blind spot when severe so as to form a pestle shaped defect. It was closely similar to the scotomas of alcohol, tobacco and lead. In Yamaguchi's case (283) slight paresthesias of all extremities and slight edema of the feet preceded the onset of dimness of vision. The patella reflex was lost. There is no mention of motor weakness or muscular tenderness. In Yamamoto's case (284) a 21 year old patient who had had kakke 7 years earlier, developed fever, chills and pains in the head, and the next day experienced edema and paresthesias of the extremities and trunk. Anorexia and sense of oppression accompanied the development of central scotoma. Kagawa (115) has published a detailed analysis of 200 cases of retrobulbar neuritis studied in Japan. Of these 95 were associated with "beriberi" 61 were females who developed the condition during lactation without signs of beriberi, 28 developed retrobulbar neuritis and "beriberi" during lactation, and the remainder were associated with other conditions (syphilis, tobacco intoxication, hysteria). It is shown that the course and type of amblyopia is the same whether occurring alone during lactation, or in association with beriberi. Twenty-five of 75 males and 5 of the 19 females had had beriberi 2 to 9 times, and the amblyopia had in them developed usually after the second attack of beriberi. The intensity of the amblyopia did not however correspond with the degree of development of other symptoms. Retrobulbar neuritis was rarely found in severe beriberi, and occurred at all times of the year, whereas beriberi appeared in the summer. Kagawa nevertheless concluded that the same deficiency could cause at one time beriberi, at another amblyopia, and felt that straining the eyes in fine work determined the localization of effect in the optic nerves.

The retrobulbar neuritis of lactation has been described in European literature, Schöppe (194), Langenbeck (127), where a variety of intoxications or infectious causes has been suggested. A third of Langenbeck's cases of retrobulbar neuritis in pregnancy, lactation or menstruation subsequently developed multiple sclerosis. This disease is seldom the cause of a *symmetrical* bilateral retrobulbar neuritis and the scotoma is usually centro-caecal, not central. Sinus disease is now no longer considered a cause of symmetrical scotoma.

Critical examination of the data provided by Kagawa reveals scant evidence of beriberi in relation to "beriberi amblyopia." The condition is that called "latent beriberi" by some authors. Cardiac symptoms were not present in many cases and when present were very slight (some enlargement to right in 53 per cent, to left in 31 per cent). The pulse rate averaged 77. There was a trace of edema in 40 per cent, severe in 2 cases. The knee jerks were normal or exaggerated in 53 per cent, absent in only 18 per cent, and ankle jerks absent in 47 percent. There was usually slight hypalgesia extending to the abdomen, back of the hands and around the mouth in some. There was *no motor weakness or tenderness*. Nine cases had a severe ataxia and will be mentioned further below. Extensive investigations of spinal fluid, blood sugar, blood catalase and basal metabolism revealed nothing remarkable.

Kagawa subjected 3 patients recovering from retrobulbar neuritis to an experimental diet deficient in thiamin which caused death in pigeons within 27–42 days. The first developed a very severe peripheral neuritis with cardiac symptoms (which she had not had before), and the diet had to be abandoned on the 80th day. Vision continued to improve throughout this severe test. The second patient had had hypesthesia of the lower limbs before the onset of retrobulbar neuritis and both had improved with treatment in hospital. The deficient diet was then given and by the 45th day the ankle jerks were lost, hypesthesia had developed, and the heart was enlarged. Vision nevertheless continued to improve. On the 56th day vision suddenly lessened in both eyes, and on the 60th day oryzanin extract (rice polishings) was added to the defective diet. By the 70th day the hypesthesia lessened but vision continued to worsen to the 80th day when there was sudden recovery beyond the previous optimum in 24 hours. In the third experiment the patient had a history of recovery from intense edema (?beriberi) in 1928, to develop amblyopia in 1929. Partial visual recovery (to 0.7 R, 0.5 L) was obtained by hospital treatment before the experimental diet was instituted. On the 48th day edema began to develop, and by the 59th day hypesthesia over the legs and hands and tenderness of the calves. Vision continued to improve. On the 80th day the ankle jerks were no longer obtained and vomiting began. Suddenly vision dropped from 1.2 R, 0.9 L to 0.7 R, 0.8 L. Oryzanin extract was administered from 80th day onwards and all signs and symptoms improved so that by the 96th day vision was 1.2 R, 1.2 L.

From these remarkable experiments Kagawa concludes that there is a close relation between beriberi and retrobulbar neuritis. The evidence would appear to be capable of the reverse interpretation, that even if a severe beriberi neuritis were experimentally induced there is difficulty in causing relapse of retrobulbar neuritis, and then only in a stage of more general deficiency. Kagawa treated retrobulbar neuritis with oryzanin extract of rice polishings and claimed very good results if treatment were commenced within one month of onset, slower recovery if after 2 months, and variable or no recovery after 3 months. Rice polishings may be expected to contain other elements of the B complex besides thiamin, and Itoh (110) remarks on the occurrence of pellagra in Japanese on a

diet of polished rice; with relief of all signs (including stomatitis, cutaneous eruption and psychosis) by feeding rice polishings. The ninth case reported by Itoh had a peripheral neuritis "resembling beriberi," but there is no mention of visual disorder. The same objection applies to the claim that the retrobulbar neuritis of lactation is a variety of beriberi on account of its response to treatment by oryzanin extract. In Kagawa's series cardiac signs were usually entirely lacking, the tendon jerks exaggerated, and in some ankle clonus or ataxia was present. Finally, none of the suckled children developed infantile beriberi. This condition and the deafness associated with it must be accounted a deficiency disorder separate from beriberi.

Deafness is recorded in scarcely a single case of classical beriberi. In hyperemesis gravidarum deafness may accompany the nystagmus which is so prominent in this condition, and retrobulbar neuritis has been recorded in a number of cases (218) (238) (106). Though the peripheral neuritis which accompanies hyperemesis gravidarum may be identical in its distribution of paralysis, tenderness and sensory loss with that of beriberi, retrobulbar neuritis and deafness are more common sequelae when peripheral neuritis did not occur (106).

Ataxia is difficult to estimate in the presence of great muscular weakness, but many writers following Scheube (192) are insistent that the gait of beriberi, though awkward and high stepping, is not ataxic. Vedder (245) described a late stage, just before all power of walking is lost, when ataxia with Romberg's sign appeared. The same author as a result of his experience with forms of the disease observed in the Phillipines stated that "during convalescence the muscles become spastic and the gait frequently resembles that of spastic spinal paralysis." He likened the "spasticity" to the similar spasticity of the legs observed in the recovering stage in fowls which developed polyneuritis from feeding on polished rice and were then treated with natural rice (42). A similar delayed spasticity has been seen in thiamin deficiency in dogs (57) (229) and will be discussed with experimental evidence. Scheube (191) also described "late spasticity" but in terms that indicate fixed shortening (contracture) of the calf muscles. "Beriberi ataxia" has been observed in Japan (Shirotori 1917, Ohashi 1920, Ushikura 1920), Tsuji (1925) and others quoted by Kagawa (115), and is then seen in patients who have developed retrobulbar neuritis (Shimazono (205) and Kagawa (115)). In Kagawa's account the onset of the ataxia in 9 cases was earlier than the retrobulbar neuritis in 5, concurrent in 1, and at intervals of 5 to 30 days after the retrobulbar neuritis in 3. Though the ataxia is here called "beriberi" it is to be noted that there was no motor paralysis, and hypesthesia was slight in all except 2 when it extended over all extremities, up the trunk, and in one around the mouth. Sense of position and vibration was gravely impaired in the lower limbs in all, and in the upper limbs in 2. Muscular tenderness is not mentioned. Edema was "slight." The knee jerks were still present in 2, absent in the others. Deafness and tinnitus were present in 2, angular stomatitis in 4. This condition has therefore obvious differences from the distal neuritis of beriberi and though Kagawa states that recovery or great improvement followed treatment with oryzanin extract (uncrystallized extract of rice polishings) with a full diet, we doubt its relationship to true beriberi.

The anesthesia of beriberi follows a course which has been well recognized for over a century. Beginning over the outer side of the leg the affected area spreads to the dorsum of the foot and round the leg. Spread to the thigh occurs about the same time as numbness of the fingers is experienced. Further progression of the disease is then shown by impairment of sensation over the abdomen (138) (205). Even in the most severe cases the numbness and loss of sensation does not usually extend from the proximal thigh over the groin. These characteristic areas are shown in a diagram by Miura (156) and Shimazono (205) that also depicts loss of sensation over the lips. Numbness round the mouth was described by Ridley (185) in 1818 in relation to an endemic disease in Ceylon characterized by edema, vomiting, dyspnea, suppression of urine and syncope, and called "beriberi." The scanty description of nervous symptoms would appear to fit the pellagroid disorder common in Ceylon to the present day, described by Nicholls (169, 170) and discussed further below. Bentley (20) describes 4 cases with numbness of the lips, all atypical in some respect. Three had great muscular tenderness and weakness of the dorsiflexors of the ankle but also had severe glossitis. The fourth suffered from retrobulbar neuritis and little if any weakness. Malcolmson (138) said numbness of the lips was unknown in India but considered any affection of the cranial nerves atypical. He mentioned exceptional cases where numbness involved both limbs and trunk and face with but little loss of power, and where ataxia was a prominent feature of the disease. Pekelharing and Winkler (177) state they were unable to find loss of sensation around the mouth. Kagawa (115) found numbness of the lips a feature of the hypesthesia of cases having retrobulbar neuritis whose other disorders we do not accept as beriberi. They were probably examples of special syndromes with prominent numbness and ataxia, but with little objective loss of sensation to touch and pain, to be mentioned below.

Numbness and ataxia, especially when loss of position and vibration sense is disproportionately severe are characteristic of selective degeneration of the dorsal columns of the spinal cord. Loss of tendon jerks can also occur from disease of the dorsal columns in disease such as Friedreich's ataxia or combined system disease. Dürck (67), Jeanselme (111), Yamagiva (282), Pekelharing and Winkler (177), Wright (279), Shimazono (206) Vedder (246) and Rodenwalt (188) found ascending degeneration of Goll's tract in a small proportion of cases of beriberi polyneuritis and then only such as could be fully accounted for by ascending degeneration of the concurrently affected dorsal nerve roots. Similar degeneration is described in beriberi in the monkey (165). There is therefore no evidence that a primary degeneration of the dorsal columns can be responsible for numbness and ataxia in the course of beriberi polyneuritis.

Further differences in type of beriberi have also long been recognised. The "wet" edematous type, first described ("barbiers" "shoshin") as a separate disease, and recognised as a variant of beriberi by Malcolmson (138) and Vinson (251) appears often to be confused with nutritional edema. "Sailing ship beriberi" in European sailors on diets of white bread and pork was commoner in the long voyages of earlier days, and confused with scurvy with which it was frequently associated (171) (101) (13). Norwegian and German cases exhibited

however a difference from Asiatic beriberi, for though anorexia, nausea, constipation, dropsy and paresthesias of the feet developed, the thigh muscles were sometimes severely affected, with loss of knee jerk, yet with little weakness of pretibial muscles (199) (171). Though weakness of extension of the knee certainly occurs in the polyneuritis of beriberi, and is the basis of the weakness revealed by the "squatting test" (253) it is seldom severe, and is less in degree than dorsiflexion of the ankle. Beriberi in rice-eating Asiatic seamen followed the usual course of the disease (35). The fishermen described by Putnam (183) ate molasses, fried pork and pancakes and developed characteristic distal polyneuritis with cardiac symptoms.

Beriberi with the usual high mortality occurred in mental hospital patients on diets not containing rice in 3 different countries in 1897. An outbreak in Ireland is described by Norman (172). Edema, cramps, tachycardia and cardiac insufficiency were accompanied by dropped feet and a prominent ascending numbness. In some patients burning of the feet was prominent, amblyopia occurred in many cases and edema of the optic disc was found in some. Loss of voice was occasionally encountered. Weakness of the extensors of the knee was specifically noted, and a third nerve paralysis in one case. In 1897 Bondurant (26) also described cases seen in the State Insane Hospital, Tuscaloosa. He also described burning sensations in the feet as a prominent and early symptom, and noted facial paralysis in 4 cases, aphonia in 1 and dysphagia in another. The usual distal neuritis and cardiac symptoms were universal. Chantemesse and Raymond (43) described a further outbreak in France, in which the cutaneous and alimentary changes of pellagra were accompanied by tachycardia, edema, symmetrical cramps and ascending numbness. Ataxia was followed by footdrop, but loss of sphincter control and bulbar paralysis including amblyopia supervened. Autopsy in 2 cases revealed degeneration of the peripheral nerves, vacuolated anterior horn cells, but no changes in the dorsal or lateral columns of the spinal cord.

In other countries where neuritic beriberi arose from diets which did not include rice, retrobulbar neuritis also occasionally complicated the picture as in the case of Mossé and Destarac (163) from Senegal, and the Brazilian cases described by Silva Lima (208) and reviewed by Féris (75). Silva Lima also described cases with strabismus, dysarthria and dysphagia. The Brazilian "beriberi" of Lovelace (132) was characterized by exaggeration of knee jerks with sudden collapse and death which recalls Sebrell's acute experimental riboflavine deficiency (198).

Little (130) described 220 cases in the inhabitants of Newfoundland and Labrador, of whom 83 had paralysis, resulting from a diet of white wheaten flour and fish. He cited one patient who developed optic neuritis, sixth nerve paralysis, and later polyneuritis. Cardiac disorder, which he appears to consider synonymous with vagal paralysis, was common, but it is uncertain from the description how much simple edema was called beriberi. It is stated that hens fed on the same white flour developed paralysis. Aykroyd (15) also found the optic and oculomotor nerves occasionally affected in the course of a painful

polyneuritis with footdrop but without cardiac changes, in Labrador. The diet had included much white flour. In the descriptions of some authors (e.g. Earle (69)) cramps in the legs are accepted as evidence of polyneuritis, a procedure which has led to misunderstanding. Not only are cramps foreign to tropical beriberi, but when they have been reported in association with a distal polyneuritis the diet has contained wheaten flour as cereal and not rice. It is under these circumstances that amblyopia, aphonia, abnormal distribution of sensory loss, ataxia and other symptoms, including the muco-cutaneous lesions pellagra appear, in association with the polyneuritis of beriberi.

If laryngeal paralysis and sometimes facial nerve paralysis can complicate acute fulminating types of beriberi, it is natural to enquire whether retrobulbar neuritis and ataxia may not arise in even more acute states, and thus possibly account for some of the variants of the disease described above. The clouding of consciousness with nystagmus, ophthalmoplegia, and ataxia first described by Wernicke (255) in 1881 as polioencephalitis superior is now generally accepted to be the result of acute thiamin deprivation. Its morbid anatomy differs from that of beriberi in the degree of cellular changes in the nuclei of the brain stem and gray matter of the mid-brain and mamillary region, and the vascular stasis and hemorrhage which accompanies these. Ataxia often accompanies the onset of Wernicke's syndrome, is slow to recover and its relation to thiamine deficiency is doubtful (232) (29). This ataxia may be accompanied by signs of the more usual distal neuritis of beriberi, with muscular tenderness and pretibial weakness, but tends to remain after these have recovered. Though its origin is open to question, such ataxia has fair correlation in degree with the severity of the "encephalitis" and polyneuritis. Were the retrobulbar neuritis, ataxia and deafness with which we are here concerned regularly preceded by the Wernicke's syndrome their pathology might be linked with the cerebral vascular disorders which distinguish it from beriberi. These nervous symptoms in our cases were however of different onset. Though Spillane (214) cites a case where a "marked degree of polyneuritis" developed during treatment of Wernicke's encephalopathy by intramuscular thiamine, without further details except that the patient was left with a residual retrobulbar neuritis, nerve deafness, altered voice and ataxia, some special circumstance and some unusual feature of the "polyneuritis" must be suspected. Some of our cases of spastic paraplegia had an initial encephalopathy which however differed from Wernicke's disease.

If all the phenomena that have been described in association with beriberi, however rarely, are included under the term "beriberi" its value becomes synonymous with all deficiency disease and much besides. The classical descriptions clearly establish the cardiac condition and a clear-cut distal polyneuritis where foot-drop with pronounced muscular tenderness, loss of ankle jerk and peripheral hypesthesia are succeeded by wrist drop. All variants and epiphenomena are open to suspicion, not only in their relationship to "beriberi," but even that they are truly neuritic. The use of the term "nutritional polyneuritis" inclusive of beriberi, alcoholic polyneuritis, polyneuritis of pregnancy and diabetic polyneuritis (227) with inclusion of burning of the soles of the feet and

persistent loss of vibration sense as prominent features of the condition may be of value in clinical usage. To call all these conditions "beriberi" only leads to pathological and therapeutic confusion. Arguments for and against the existence of thiamin deficiency in peripheral nerves (145) have accepted the premise that nearly all forms of peripheral neuritis are the same. The production of burning in the feet on the 5th day and cramps in the calves on the 7th day of experimental thiamin deficiency in human volunteers by Jollife and his associates (114) scarcely merits the term "polyneuritis" some have applied to the condition. Its significance remains to be explained, but it is extremely doubtful if it has any relation to true beriberi. Lastly, the assumption by some (180) (145) that pain after walking any distance in beriberi can be likened to intermittent claudication, and therefore indicates vascular change, is unwarranted in a condition where even slight contacts also cause pain.

2. Pellagra

Whereas the nervous symptoms under discussion bear doubtful, rare, and distant relationship to beriberi it is found that many of them have long had recognition in the symptom-complex of pellagra. Vertigo has been a classical feature of this condition since the earliest accounts. Pains in the hands and feet are common complaints. Billod described paraplegic disorders in 1865 (24). Taylor and Wood (236) state that a staggering gait is an early complaint which frequently persists through the whole course of the disease and is the last remnant in the recovering case. Besides the tremors and spasms which are so prominent in advanced states, increased tendon jerks, spastic rigidity in the lower extremities with ataxic gait and positive Romberg's sign are commonly described (24) (240) (19) (131) (100) (236) (23). In the "typhoid pellagra" of Belmondo (19) spastic changes with dysarthria and tremors characterize the final delirium. But it has also long been recognized that spastic or ataxic disorders of the lower limbs, and affections of the optic and auditory nerves, may in some patients occur early in the course of the disease. The plantar reflex is occasionally extensor, often on one side only. Roberts (187) found ataxia in 12 of 60 cases, vertigo in 20, slurred speech in 14. Deafness was present in 8 and vision impaired in 3. Tinnitus frequently accompanied the onset of deafness. Ellinger *et al* (71) found clinical evidence of spinal cord lesions in 10 of 39 pellagrins from Upper Egypt, and only in 4 per cent of patients from the Nile Delta. Lombroso (131) mentioned optic atrophy in 3 of 36 cases examined by Manfredi. Bietti (22) in 1901 found pallor of the optic disc in some cases but could not find any histological changes in the optic nerve in 2 cases followed to autopsy. He was inclined to believe that retinal degeneration accounted for amblyopia. Whaley (256) found optic atrophy in 3, and optic neuritis in 3, of 35 pellagrins. Bouchard (28) first described pigmentary changes in nerve cells and degeneration of the dorsal and lateral columns of the spinal cord in pellagra in 1864. Tonnini (240) found spasticity and exaggeration of reflexes common in the third stage of pellagra and described degeneration of the lateral columns of the cord in addition to the well known pigmentary degeneration of the anterior

horn and cortical cells. Langworthy (128) described diffuse degeneration of the lateral columns, with severe cell changes, in an acute case. Tuczek (242) saw combined, often vacuolated, degeneration of both lateral and dorsal columns of the spinal cord in 6 of 8 cases examined, the dorsal columns alone in 2. Belmondo (19) and Gaucher and Sergent (81) found degeneration in the dorsal columns, heavier in the cervical region. Sandwith (189) described diffuse degeneration of the posterior columns in 2 of 3 Egyptian cases. Lukás and Fabinyi (133), Marinesco (141), Anderson and Spiller (7), Box and Mott (30), Wilson (261), Singer and Pollock (210), McCowan (137), Greenfield and Holmes (93), and Pauly and Deprecq (176) all found diffuse degeneration in the lateral and posterior columns. Pentshew (178) found hyaline changes in the capillaries and considered that this and the patchy nature of degeneration indicated primary vascular factors. Winkleman (263) deals chiefly with the cell changes. Guillain and his colleagues (95) describe an example of severe combined degeneration of dorsal and lateral columns where spastic paraplegia long preceded cutaneous changes and stomatitis. Wood (275) pictures a severe vacuolated degeneration of the anterolateral and dorsal columns closely resembling subacute combined system disease. There is no mention of anemia, and the patient was aged 17 years. Wilson (261) found that some cases closely resembled combined system disease. Other accounts of the spinal degeneration in pellagra indicate a diffuse degenerative process unlike that accompanying pernicious anemia, and Anderson and Spiller (7) are particularly emphatic concerning this difference. Loss of vibration sense, which is a prominent feature of subacute combined system disease, is held to be prominent in pellagra by Taylor and Wood (236), but is not mentioned by others.

States of spastic weakness of the lower limbs with fascicular twitchings in the upper limbs are commonly described in terminal stages of classical pellagra. They appear to be due to the widespread scattered pigmentary degeneration of nerve cells. The more chronic spastic changes in the limbs do not resemble amyotrophic lateral sclerosis, for the dorsal columns are nearly always involved. The cell changes in the cerebral cortex in pellagra are more generalized and show ballooning of cells, and ill defined pigmentary changes, whereas those of amyotrophic lateral sclerosis are localized to the motor region and seldom show intermediate changes. Though muscular atrophy, fasciculation and twitchings are commonly present in late stages of pellagra, these are more diffuse and do not exhibit the slow spread of amyotrophic lateral sclerosis. Cases of pellagra with close clinical resemblance to amyotrophic lateral sclerosis (167), (23) are excessively rare and probably coincidence. Such changes in the peripheral nerves as have been described are limited to scattered loss of occasional fibers in anterior and posterior nerve roots (186) (121) associated with increase in π-granules (261) and irregular changes in the staining reaction of otherwise intact myelin by the Marchi method. No severe polyneuritis is commonly associated with classical pellagra, but the scattered degeneration of isolated peripheral nerve fibers corresponds with the scattered degeneration of isolated ventral horn and dorsal root ganglion cells (128). On the other hand cases of pellagra

persistent loss of vibration sense as prominent features of the condition may be of value in clinical usage. To call all these conditions "beriberi" only leads to pathological and therapeutic confusion. Arguments for and against the existence of thiamin deficiency in peripheral nerves (145) have accepted the premise that nearly all forms of peripheral neuritis are the same. The production of burning in the feet on the 5th day and cramps in the calves on the 7th day of experimental thiamin deficiency in human volunteers by Jollife and his associates (114) scarcely merits the term "polyneuritis" some have applied to the condition. Its significance remains to be explained, but it is extremely doubtful if it has any relation to true beriberi. Lastly, the assumption by some (180) (145) that pain after walking any distance in beriberi can be likened to intermittent claudication, and therefore indicates vascular change, is unwarranted in a condition where even slight contacts also cause pain.

2. Pellagra

Whereas the nervous symptoms under discussion bear doubtful, rare, and distant relationship to beriberi it is found that many of them have long had recognition in the symptom-complex of pellagra. Vertigo has been a classical feature of this condition since the earliest accounts. Pains in the hands and feet are common complaints. Billod described paraplegic disorders in 1865 (24). Taylor and Wood (236) state that a staggering gait is an early complaint which frequently persists through the whole course of the disease and is the last remnant in the recovering case. Besides the tremors and spasms which are so prominent in advanced states, increased tendon jerks, spastic rigidity in the lower extremities with ataxic gait and positive Romberg's sign are commonly described (24) (240) (19) (131) (100) (236) (23). In the "typhoid pellagra" of Belmondo (19) spastic changes with dysarthria and tremors characterize the final delirium. But it has also long been recognized that spastic or ataxic disorders of the lower limbs, and affections of the optic and auditory nerves, may in some patients occur early in the course of the disease. The plantar reflex is occasionally extensor, often on one side only. Roberts (187) found ataxia in 12 of 60 cases, vertigo in 20, slurred speech in 14. Deafness was present in 8 and vision impaired in 3. Tinnitus frequently accompanied the onset of deafness. Ellinger *et al* (71) found clinical evidence of spinal cord lesions in 10 of 39 pellagrins from Upper Egypt, and only in 4 per cent of patients from the Nile Delta. Lombroso (131) mentioned optic atrophy in 3 of 36 cases examined by Manfredi. Bietti (22) in 1901 found pallor of the optic disc in some cases but could not find any histological changes in the optic nerve in 2 cases followed to autopsy. He was inclined to believe that retinal degeneration accounted for amblyopia. Whaley (256) found optic atrophy in 3, and optic neuritis in 3, of 35 pellagrins. Bouchard (28) first described pigmentary changes in nerve cells and degeneration of the dorsal and lateral columns of the spinal cord in pellagra in 1864. Tonnini (240) found spasticity and exaggeration of reflexes common in the third stage of pellagra and described degeneration of the lateral columns of the cord in addition to the well known pigmentary degeneration of the anterior

horn and cortical cells. Langworthy (128) described diffuse degeneration of the lateral columns, with severe cell changes, in an acute case. Tuczek (242) saw combined, often vacuolated, degeneration of both lateral and dorsal columns of the spinal cord in 6 of 8 cases examined, the dorsal columns alone in 2. Belmondo (19) and Gaucher and Sergent (81) found degeneration in the dorsal columns, heavier in the cervical region. Sandwith (189) described diffuse degeneration of the posterior columns in 2 of 3 Egyptian cases. Lukás and Fabinyi (133), Marinesco (141), Anderson and Spiller (7), Box and Mott (30), Wilson (261), Singer and Pollock (210), McCowan (137), Greenfield and Holmes (93), and Pauly and Deprecq (176) all found diffuse degeneration in the lateral and posterior columns. Pentshew (178) found hyaline changes in the capillaries and considered that this and the patchy nature of degeneration indicated primary vascular factors. Winkleman (263) deals chiefly with the cell changes. Guillain and his colleagues (95) describe an example of severe combined degeneration of dorsal and lateral columns where spastic paraplegia long preceded cutaneous changes and stomatitis. Wood (275) pictures a severe vacuolated degeneration of the anterolateral and dorsal columns closely resembling subacute combined system disease. There is no mention of anemia, and the patient was aged 17 years. Wilson (261) found that some cases closely resembled combined system disease. Other accounts of the spinal degeneration in pellagra indicate a diffuse degenerative process unlike that accompanying pernicious anemia, and Anderson and Spiller (7) are particularly emphatic concerning this difference. Loss of vibration sense, which is a prominent feature of subacute combined system disease, is held to be prominent in pellagra by Taylor and Wood (236), but is not mentioned by others.

States of spastic weakness of the lower limbs with fascicular twitchings in the upper limbs are commonly described in terminal stages of classical pellagra. They appear to be due to the widespread scattered pigmentary degeneration of nerve cells. The more chronic spastic changes in the limbs do not resemble amyotrophic lateral sclerosis, for the dorsal columns are nearly always involved. The cell changes in the cerebral cortex in pellagra are more generalized and show ballooning of cells, and ill defined pigmentary changes, whereas those of amyotrophic lateral sclerosis are localized to the motor region and seldom show intermediate changes. Though muscular atrophy, fasciculation and twitchings are commonly present in late stages of pellagra, these are more diffuse and do not exhibit the slow spread of amyotrophic lateral sclerosis. Cases of pellagra with close clinical resemblance to amyotrophic lateral sclerosis (167), (23) are excessively rare and probably coincidence. Such changes in the peripheral nerves as have been described are limited to scattered loss of occasional fibers in anterior and posterior nerve roots (186) (121) associated with increase in π-granules (261) and irregular changes in the staining reaction of otherwise intact myelin by the Marchi method. No severe polyneuritis is commonly associated with classical pellagra, but the scattered degeneration of isolated peripheral nerve fibers corresponds with the scattered degeneration of isolated ventral horn and dorsal root ganglion cells (128). On the other hand cases of pellagra